GESTATIONAL WEIGHT GAIN AND PRE-CONCEPTIONAL CARDIOVASCULAR HEALTH IN PREGNANT WOMEN WITH SYSTEMIC LUPUS ERYTHEMATOSUS

Amanda Marie Eudy

A dissertation submitted to the faculty at the University of North Carolina at Chapel Hill in partial fulfillment of the requirements for the degree of Doctor of Philosophy in the Department of Epidemiology in the Gillings School of Global Public Health.

Chapel Hill
2016

Approved by:

Anna Maria Siega-Riz

Stephanie Engel

Nora Franceschini

Annie Green Howard

Megan Clowse

ABSTRACT

Amanda Marie Eudy: Gestational Weight Gain and Pre-Conceptional Cardiovascular Health in Pregnant Women with Systemic Lupus Erythematosus
(Under the direction of Anna Maria Siega-Riz)

Systemic lupus erythematosus (SLE) is an autoimmune disease largely affecting women of childbearing age. Compared to the general population, SLE patients have a higher risk of poor pregnancy outcomes. We investigated three aspects of pregnancy in SLE patients in the Hopkins Lupus Pregnancy Cohort: a) weight gain during pregnancy, b) preconceptional cardiovascular health as a risk factor for pregnancy outcomes, and c) the effect of pregnancy on disease activity.

For the analysis of gestational weight gain (GWG), of the 211 pregnancies with available data, 34%, 24%, and 42% had inadequate, adequate, and excessive GWG, respectively, based on pre-pregnancy BMI, according to Institute of Medicine (IOM) guidelines. In exploratory analyses, differences in IOM adherence were observed by pre-pregnancy BMI, race, elevated creatinine, and pre-pregnancy blood pressure. Odds of inadequate and excessive GWG increased 12% with each 1 kg/m^2 increase in pre-pregnancy BMI. Lower maternal education was associated with increased odds of inadequate and excessive GWG.

Next, we analyzed 308 births with available preconceptional cardiovascular data, of which 56% had ideal BMI (<25 kg/m^2), 86% ideal total cholesterol (<200 mg/dL untreated), and 51% ideal blood pressure (<120/<80 mm Hg untreated). In adjusted models, overweight was associated with decreased odds of small for gestational age (OR: 0.26; 95% CI: 0.11, 0.63) compared to ideal weight, intermediate/poor total cholesterol was associated with increased odds of preterm birth (OR: 1.91; 95% CI: 0.96, 3.79), and intermediate/poor blood pressure was associated with decreased gestational age at birth (β: -0.96; 95% CI: -1.62, -0.29).

Finally, due to adverse effects of flares on pregnancy outcomes, we estimated rates of flares during pregnancy and a 1-year postpartum period compared to unexposed periods. We observed an increased rate of flares during pregnancy in stratified Cox models for PGA flare (HR: 1.59; 95% CI: 1.27,

1.96) and SELENA SLEDAI flare (HR: 1.57; 95% CI: 1.25, 1.92). The HR of flares during pregnancy compared to unexposed periods was modified by hydroxychloroquine use.

Our results demonstrated the need for interventions to improve GWG guideline adherence and pre-conceptional cardiovascular health, and the importance of continuing to monitor SLE patients for flares during pregnancy.

To my parents –
thanks for all that you do.

ACKNOWLEDGEMENTS

Writing a dissertation is a long and tedious labor of love and a task I certainly could have not accomplished without the help and support of so many individuals in my life. First, I am forever grateful for my dissertation committee, Drs. Anna Maria Siega-Riz, Stephanie Engel, Nora Franceschini, Annie Green Howard, and Megan Clowse, for their expertise, kindness, and guidance. Thank you for agreeing to delve into the world of lupus pregnancies with me and for making me a better epidemiologist along the way. I also thank Dr. Michelle Petri for allowing me to use the data she has spent more than 25 years collecting.

I would be remiss to not acknowledge my friends, who cheered me on over the past six years, never complained when I canceled plans to handle a SAS crisis, and supplied care packages in times of need. Katie Holliday, Hannah Scherr, Tyler Craft, Lauren Kinney, Kara Yates, and Peter Romanov – thanks for always being there. To my friend and mentor, Deanna Hill, I'm thankful for the years we worked together and the knowledge I gained while being your research assistant (both epidemiology- and cookware-related).

Next, I thank my family. My parents for always believing in me and never being upset when I replied "just one more year" every time they asked how much longer until I finished school. My brother for printing copies of my DAGs to hang in his office, I can only assume to confuse his co-workers. To my husband-to-be, Seth Beckley, thank you for the constant support, the big hugs, and your unbelievable patience. If we can survive this, we can survive anything. Finally, I thank my grandfather, Norman Eudy, who spent his final years telling every person he encountered, stranger or not, that his granddaughter was going to be a doctor. I finally am.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

aCL	anti-cardiolipin
ACR	American College of Rheumatology
AHA	American Heart Association
ANOVA	analysis of variance
BILAG	British Isles Lupus Assessment Group
BMI	body mass index
C3	complement 3
C4	complement 4
CARDIA	Coronary Artery Risk Development in Young Adults Study
CDC	Centers for Disease Control and Prevention
CI	confidence interval
DAG	directed acyclical graph
dL	deciliter
DNA	deoxyribonucleic acid
dsDNA	double-stranded DNA
ECLAM	European Consensus Lupus Activity Measurement
GWG	gestational weight gain
HCQ	anti-malarial
HELLP	hemolysis, elevated liver enzymes, and low platelets
Hg	mercury
HR	hazard ratio
IOM	Institute of Medicine
IQR	interquartile range
IR	incidence rate
IRR	incidence rate ratio
kg	kilogram
LAI	Lupus Activity Index

LGA	large for gestational age
LMP	last menstrual period
m	meter
mg	milligram
mm	millimeter
NDAIDs	non-steroidal anti-inflammatory drugs
NHANES	National Health and Nutrition Examination Survey
OR	odds ratio
PEA	physician's estimate of lupus activity
PEPP	Pregnancy Exposures and Preeclampsia Prevention
PGA	Physician's Global Assessment of disease activity
PRAMS	Pregnancy Risk Assessment Monitoring System
PY	person-years
SD	standard deviation
SDI	Systemic Lupus International Collaborating Clinics/American College of Rheumatology (SLICC/ACR) Damage Index
SGA	small for gestational age
SLAM	Systemic Lupus Activity Measure
SLE	systemic lupus erythematosus
SLEDAI	Systemic Lupus Erythematosus Disease Activity Index
SLICC	Systemic Lupus International Collaborating Clinics
US	United States
UK	United Kingdom
WHO	World Health Organization

CHAPTER 1: INTRODUCTION

Systemic lupus erythematosus (SLE) is an autoimmune disease which largely affects women, with disease onset typically occurring between the childbearing ages of 15 and 44 (1). In the United States, the most recent analyses of population-based registries in Georgia and Michigan estimate the overall age-adjusted prevalence to be 73 per 100,000 persons (~128 per 100,000 women) (2, 3).

Pregnancy remains contraindicated in SLE patients with severe end-organ manifestations of SLE (e.g., kidney, heart, brain) or in patients who have experienced a severe disease flare within the previous six months (4). Complications during pregnancy in women with SLE are quite common, with up to 76% of women experiencing complications, including disease flares, worsening or new onset of kidney failure, hypertension, preeclampsia, or pulmonary embolism (5).

Compared to women in the general population, women with SLE have a higher risk of poor pregnancy outcomes, including four times the risk of preterm deliveries and three times the risk of fetal loss (6, 7). In SLE patients, the presence of thyroid disease, kidney disease, and certain autoantibodies are associated with an increased risk of poor pregnancy outcomes. There are, however, a number of risk factors associated with poor pregnancy outcomes that have not been examined in the population of women with SLE.

Gestational weight gain (GWG) has been shown to be associated with preterm birth, small for gestational age (SGA) and large for gestational age (LGA) in the general population, with pre-pregnancy weight being an important modifier (8). Previous research has found that among women who are underweight, less than ideal GWG is associated with preterm birth, while exceeding the IOM guidelines is associated with preterm birth in women of all pre-pregnancy BMI categories (9, 10). The vast majority of women in the general population do not meet the IOM guidelines for weight gain, with one study finding that 17% of mothers had inadequate, 31% had adequate, and 53% had excessive weight gain (11). It is currently unknown how many women with SLE meet the Institute of Medicine (IOM) recommendations for GWG and the effect of insufficient GWG on pregnancy outcomes in this population.

This dissertation investigated three interrelated aspects related to pregnancy in women with SLE not previously examined: a) weight gain during pregnancy, b) pre-conceptional cardiovascular health as a risk factor for pregnancy outcomes, and c) the effect of pregnancy on disease activity. The knowledge obtained from this research will provide a basis for understanding the effects of SLE on pregnancy, as well as the effect of pregnancy on SLE. We used data from the Hopkins Lupus Pregnancy Cohort of 515 pregnancies that occurred over a period of almost 30 years.

Specifically, we investigated the following aims:

Specific Aim 1: To estimate the proportion of pregnant women with systemic lupus erythematosus (SLE) who meet the Institute of Medicine (IOM) guidelines for gestational weight gain (GWG) and to determine factors associated with adherence to IOM guidelines for GWG.

Sub-Aim 1a: To estimate gestational weight gain trajectories for women with SLE.

Specific Aim 2: To estimate the effect of preconceptional cardiovascular health, as measured by blood pressure, total cholesterol and body mass index, on preterm birth and fetal growth (birth weight for gestational age z-score) in women with SLE.

Specific Aim 3: To estimate the effect of pregnancy on disease activity (i.e., disease flares) in SLE using a Cox proportional hazards model.

Sub-Aim 3a: To compare traditional methods for estimating the incidence of disease flares to the estimates from counting process and stratified Cox proportional hazards models.

Sub-Aim 3b: To perform a sensitivity analysis excluding women without a pregnancy from the study population.

CHAPTER 2: LITERATURE REVIEW

Systemic Lupus Erythematosus

Systemic lupus erythematosus (SLE) is an autoimmune rheumatic disease that affects a wide range of organ systems, including the skin, kidney, heart, lungs, central nervous system and musculoskeletal system. SLE is diagnosed according to the American College of Rheumatology (ACR) criteria (Appendix 1), a list of 11 measures, of which a patient must meet at least four of the criteria in order to be diagnosed with SLE (12, 13).

In the United States, the annual incidence of SLE is approximately 5 cases per 1,000 persons (2, 3). Women have a higher prevalence of SLE than men and are typically diagnosed at a younger age than men, most often during the childbearing years (ages 15 – 44 years) (14, 15). A racial/ethnic discrepancy is apparent in SLE, with African Americans, Asians, and Hispanics having a higher prevalence and incidence of SLE compared to Caucasians (16-35).

SLE is typically treated with a multi-drug combination of corticosteroids, anti-malarials, immunosuppressants, and non-steroidal anti-inflammatory drugs (NDAIDs) (36). During pregnancy, some of these medications that are toxic to the fetus need to be stopped or have the dose reduced in order to protect the fetus. Due to concerns surrounding the treatment effects on the fetus, a challenge of treating SLE during pregnancy is that changes in medications may lead to an increase in SLE disease activity, which could also lead to a poor pregnancy outcome (37).

Hydroxychloroquine (HCQ), an anti-malarial, is recommended for continued use during pregnancy (38). HCQ use during pregnancy appears to be beneficial to the mother, with a study of SLE patients reporting higher disease activity and flares in women who stopped taking HCQ compared to women who continued to take HCQ throughout pregnancy, thus providing evidence that HCQ use should not be discontinued during pregnancy (39).

Corticosteroid use during pregnancy should be limited to the lowest dose possible to control disease activity. Use of corticosteroids has been found to increase the risk of preterm birth and possibly

restrict fetal growth (40-43). Azathioprine, an immunosuppressant, can be used during pregnancy if limited to a maximum daily dose of 2 mg/kg/day. Higher doses during pregnancy can increase the risk of fetal blood cell reduction (cytopenia; e.g. anemia, thrombocytopenia, leucopenia, and pancytopenia), and immune suppression, which will increase the susceptibility to infections (37, 38). Other immunosuppressants, such as cyclophosphamide, methotrexate, and mycophenolate, should be avoided during pregnancy, as first trimester exposure can lead to birth defects (36, 37).

Pregnancy Outcomes in SLE & Risk Factors for Poor Pregnancy Outcomes

It was previously recommended that women with SLE avoid pregnancy, as the risk for poor fetal and maternal outcomes was high. Over the past several decades as the treatment and management of SLE has improved, so have fetal and maternal outcomes in pregnancies to women with SLE (44). It is currently advised that women with SLE consult with their rheumatologist prior to becoming pregnant for preconception counseling to determine factors that could increase the risk of pregnancy complications, such as severe organ system damage, high disease activity, antiphospholipid syndrome, anti-Ro or anti-La antibodies, or medications that may harm the fetus (4).

Standard obstetrical care dictates close monitoring of women throughout pregnancy for changes in disease activity and kidney function, with regular monitoring of blood to assess cell counts, inflammatory changes and renal function, urine for protein and cells that would signify lupus nephritis, and frequent measurements of blood pressure to detect preeclampsia or imminent kidney flares (45). For women who are anti-Ro or anti-La antibody positive, which are found in up to 40% of women with SLE, repeated ultrasounds of the fetus's heart between 18 and 28 weeks of gestation should be conducted to detect congenital heart block (4).

Fetal Loss

Fetal loss is defined by the Centers for Disease Control and Prevention (CDC) as the "spontaneous intrauterine death of a fetus at any time during pregnancy" and can be divided into spontaneous miscarriages and stillbirths (46). Spontaneous miscarriages, also known as miscarriages or spontaneous abortions, are intrauterine fetal deaths at a gestational age when the fetus would not be able

to survive outside of the uterus, whereas stillbirths are intrauterine fetal deaths at a gestational age when a fetus would be able to survive outside of the uterus (47). The gestational age cut-point used to distinguish between spontaneous miscarriages and stillbirths varies by state, country and study, ranging from 20 to 28 weeks of gestation (46, 47).

Presently, the majority of SLE pregnancies, 66 to 95% depending on the study population, result in a live birth (6, 7, 39, 48-54); however, previous research has shown that women with SLE have poorer pregnancy outcomes compared to women in the general population. In women with SLE, the frequency of spontaneous miscarriage (loss of pregnancy prior to 20 weeks gestation) ranges from 6 to 22%, and the frequency of stillbirth (loss of pregnancy after 20 weeks gestation) ranges from 0 to 12% (Table 1) (7, 39, 48-57). Comparatively, the CDC estimates that 17% of pregnancies to women of all ages in the US end in a fetal loss (spontaneous miscarriage or stillbirth) (58). The majority of the data for SLE pregnancies comes from prospective cohorts, which can under-count early pregnancy loss if a woman suffers the loss before she visits her physician to be enrolled in the study.

Table 1. Frequency of spontaneous abortions, stillbirths and fetal loss in SLE pregnancy

Reference, Year	*Country*	*# of Pregnancies*	*Spontaneous Abortion Definition*	*Spontaneous Abortions*	*Stillbirths*	*Fetal Loss*
Ambrosio 2010 (48)	Portugal	136	<20 weeks	5.9%	0.0%	5.9%
Andrade 2008 (55)	US, Puerto Rico	102	<20 weeks	20.5%	4.9%	25.5%
Cavallasca 2008 (51)	Argentina	72	<20 weeks with fetal weight <500 g	6.9%	8.3%	15.3%
Clowse 2006 (39)	US	257	<20 weeks	6.6%	7.4%	14.0%
Cortes-Hernandez 2002 (53)	Spain	103	<20 weeks	14.6%	11.7%	26.2%
Georgiou 2000 (54)	Greece	59	<21 weeks	15.3%	1.7%	16.9%
Gladman 2010 (57)	Canada	193	<20 weeks	21.8%	3.1%	24.9%

General risk factors for spontaneous miscarriage, in women with or without SLE, include increased maternal age and co-morbidities such as hypothyroidism or uncontrolled diabetes. Risk factors for stillbirths include increased maternal age, obesity, smoking and diabetes (47). In SLE, increased

disease activity and co-morbidities such as kidney disease, hypertension, antiphospholipid syndrome, heart failure, and pulmonary disease are associated with an increased risk for fetal loss (4, 7, 53, 55, 59).

Preterm Birth

Preterm birth is defined as delivery prior to 37 completed weeks of gestation. In the general population, approximately 12% of births in the United States are preterm (60). The rate of preterm births in the US increased by more than 20% from 1990 to 2006, although more recent reports indicate that the rate is slowly declining after its peak in 2006 (61). A racial disparity is apparent in the rate of preterm birth, with 17.5% of births to non-Hispanic black mothers in 2008 being preterm, compared to 11.1% and 12.1% in non-Hispanic white and Hispanic mothers, respectively (61). Although the majority of preterm infants survive, the risks of mortality and morbidity (such as neurological, respiratory, gastrointestinal, and kidney systems development) are higher in preterm infants compared to infants born at term (62).

Within the overarching outcome of preterm birth, there are subtypes: spontaneous preterm labor, premature rupture of membranes, and medically indicated preterm birth. In the general population, the largest proportion of preterm births is due to spontaneous labor (45%), and the pathways that lead to each type of preterm delivery vary (62), though some overlap. Medically indicated preterm births occur when a baby is intentionally delivered before 37 weeks due to medical complications in the mother or the fetus. In addition to the high burden of morbidity due to preterm birth, the costs associated with a preterm delivery increase substantially for each week prior to term that an infant is delivered (63). Once study reported that for medical costs during the first 5 years of life, infants born at <28 weeks gestation accrued almost $23,000 more in hospital utilization costs compared to term infants, and infants born at 28 to 31 weeks gestation had costs almost $19,000 greater than term infants (63).

In the general population, risk factors for preterm birth include prior preterm births, low education, sociodemographic characteristics, maternal age, low BMI, multiple gestations, and infections (62). The literature reports that 8 to 53% of infants born to women with SLE are delivered preterm (Table 2) (6, 7, 39, 48-54, 64). Compared to women in the general population, the odds of preterm delivery among women with SLE was 6 times that of women in the general population (OR=6.17; 95% CI: 3.28-11.58), adjusting for instrumentation to assist in the delivery and caesarean section (65). In SLE, risk factors for

preterm birth include hypertension, increased disease activity during pregnancy, the presence of anti-cardiolipin (aCL) antibodies, and prednisone use either prior to or during pregnancy (6, 7, 51-54). Although data are limited, one study reported that 75% of preterm births in women with SLE were medically indicated (50). Reasons for a medically indicated preterm delivery in SLE, either by a caesarean section or induction of labor, include maternal high blood pressure, pre-eclampsia, proteinuria, decreased amniotic fluid volume, intrauterine growth restriction, and HELLP syndrome (hemolysis, elevated liver enzymes, and low platelets), a complication of eclampsia (6).

Table 2. Frequency of preterm birth in SLE pregnancy.

Reference	*Country*	*# of Pregnancies*	*Live Birth*	*Preterm Birth**,†*
Ambrosio 2010 (48)	Portugal	136	94.9%	24.0%
Brucato 2002 (49)	Italy	149	84.6%	19.8%
Carvalheiras 2010 (50)	Portugal	51	90.0%	17.4%
Cavallasca 2008 (51)	Argentina	72	86.1%	46%
Chakravarty 2005 (52)	US	63	87.3%	52.7%
Clark 2003 (6)	Canada	88	83.0%	38.4%
Clowse 2005 (7)	US	267	85.8%	38.0%
Cortes-Hernandez 2002 (53)	Spain	103	66.0%	27.9%
Georgiou 2000 (54)	Greece	59	66.1%	7.7%
Mecacci 2009 (64)	Italy	62	82.3%	29.4%

*Defined as <37 weeks of gestation
†Frequency among live birth infants

Low Birth Weight for Gestational Age

Low birth weight is defined as a birth weight of <2500 g, and the CDC estimates that 8% of births in the US general population in 2012 were low birth weight (66). Low birth weight infants are at increased risk for infant mortality (death within 1-year after birth) than heavier infants (53.05 deaths per 1,000 births vs. 2.21 deaths per 1,000 births, respectively) (67) and are at increased risk for complications such as respiratory distress syndrome, intraventricular hemorrhage, and necrotizing enterocolitis (68). It has been estimated that 5 to 39% of infants born to mothers with SLE are classified as low birth weight (48, 51, 53, 54). Hypertension and aCL antibodies are risk factors for delivering a low birth weight infant in SLE (53).

A methodological issue of low birth weight is that it is largely dependent on the duration of gestation, as approximately half of infants who are classified as low birth weight are born preterm (47). An alternative measure of fetal growth that takes gestational age into consideration is classifying infants as small for gestational age (SGA), defined as infants who weigh less than the 10th percentile for weight

based on their gestational age and sex. Among infants born to mothers with SLE, 16 to 23% are SGA (39, 57). Women with SLE have an increased risk of delivering a SGA infant, with one study finding the odds of delivering a SGA infant to be 2.5 times that of women in the general population (OR=2.54; 95% CI: 1.42, 4.55), when adjusted for instrumentation to assist in the delivery and caesarean section (65). The prevalence of SGA is higher among women with active kidney disease during pregnancy (defined as the presence of hematuria, pyuria, casts, and proteinuria), compared to women without active kidney disease (57).

Gestational Weight Gain

Gestational weight gain (GWG) is the amount of weight a mother gains throughout her pregnancy and is composed of maternal and fetal factors. For fetal factors, the average weight gained is 4.8 kilograms, with the fetus itself comprising an average of 3.3 kilograms (kg) of the weight gained. The remaining fetal weight gained is from the placenta (~0.7 kg) and amniotic fluid (~0.8 kg). For maternal factors, the average weight gained is 7 kilograms, largely due to increase in fat (~4.0 kg), blood volume (~1.2 kg) and extracellular fluid (~1.2 kg) (69).

The greatest increase in weight in nonfat tissues is due to water, with an increase of 6 to 7 liters of water (70). Fat is used to meet a mother's metabolic requirements and as an energy source throughout pregnancy in times of deprivation as well as for lactation postpartum. The largest amount of maternal fat is accrued during the second trimester, but fat begins to be deposited early in pregnancy (69). The increase in body fat during pregnancy has been found to vary with pre-pregnancy BMI, with one study noting that women classified as overweight and obese had a minimal increase in total body fat during pregnancy. The study also found that women who met the 1990 IOM guidelines for gestational weight gain did not amass excessive amounts of fat (71).

The pattern of weight gain during pregnancy varies greatly between women, and is most variable for obese women. One study found that the average weekly weight gain for the second and third trimesters was higher for underweight and normal weight women, compared to overweight and obese women. Additionally, all women except obese women had higher weekly rates of weight gain in the second trimester than in the third trimester (72).

In 1990, the Institute of Medicine (IOM) published guidelines on the ideal weight gain during pregnancy based on pre-pregnancy BMI, and these guidelines were updated in 2009 due to the concern of rising obesity rates in the population (Table 3) (8).

Table 3. 2009 IOM Recommendations for Gestational Weight Gain in the General Population (8)

Pre-Pregnancy BMI (kg/m^2)	Total Weight Gain (kg)	2nd and 3rd Trimester Rates of Weight Gain, mean kg/wk (range)
Underweight (<18.5)	12.5-18	0.51 (0.44-0.58)
Normal weight (18.5-24.9)	11.5-16	0.42 (0.35-0.50)
Overweight (25.0-29.9)	7-11.5	0.28 (0.23-0.33)
Obese (≥30.0)	5-9	0.22 (0.17-0.27)

The vast majority of women do not meet these guidelines for weight gain, with one study finding 53% of mothers gain more than the recommended weight, 17% gain less than the recommended weight, and only 31% gain the ideal amount of weight (11). In this analysis, women who were classified as overweight or obese were at increased risk of gaining more than the recommended amount of weight during pregnancy, compared to women with normal BMI. The proportion of women who are not meeting the guidelines for GWG is increasing. In 1997, 39.6% of women who had a pre-pregnancy BMI in the normal range exceeded the IOM's recommendations for GWG, which increased to 46.3% in 2007. The increase in the proportion of women exceeding the IOM weight gain recommendations has also been seen in women classified as being overweight or obese prior to pregnancy (8).

The appropriate amount of weight gained during pregnancy has great implications for the fetus: gaining too much weight during pregnancy has been shown to be associated with delivering large for gestational age or macrosomic (>4000 g) infants (73-89), while insufficient weight gain is associated with the delivery of a small for gestational age infant (74, 75, 78-84, 90). Gestational weight gain also has implications for preterm birth. There appears to be a U-shaped association of GWG with preterm birth, with modification by pre-pregnancy BMI (10, 91-94). Among women who are underweight according to their pre-pregnancy BMI, less than ideal GWG is associated with preterm birth, while more than ideal GWG may be associated with preterm birth in women of all pre-pregnancy BMI categories (9, 10).

Cardiovascular Health and Pregnancy

The American Heart Association (AHA)'s 2020 Impact Goals included the development of the concept of "ideal cardiovascular health," which focuses on primordial prevention and is composed of seven modifiable cardiovascular metrics: health factors (glucose, cholesterol, and blood pressure) and health behaviors (body mass index, physical activity, diet, and cigarette smoking; Table 4) (95). Meeting these metrics for ideal cardiovascular health is associated with a lower risk of cardiovascular disease, lower cardiovascular mortality rates, and lower all-cause mortality.

Table 4. American Health Association Definitions of Poor, Intermediate, and Ideal Cardiovascular Health (95)

Goal/Metric	Poor Health	Intermediate Health	Ideal Health
Current smoking	Yes	Former ≤12 months	Never or quit >12 months
Body mass index	≥30 kg/m^2	25-29.9 kg/m^2	<25 kg/m^2
Physical activity	None	1–149 minutes/week moderate intensity or 1–74 minutes/week vigorous intensity or 1–149 minutes/week moderate + vigorous	≥150 min/week moderate intensity or ≥75 minutes/week vigorous intensity or≥150 minutes /week
Healthy diet score	0–1 Components	2–3 Components	4-5 Components
Total cholesterol	≥240 mg/dL	200–239 mg/dL or treated to goal	<200 mg/dL
Blood pressure	Systolic ≥140 Or Diastolic ≥90 mm Hg	Systolic 120–139 or Diastolic 80–89 mm Hg or treated to goal	<120/<80 mm Hg
Fasting plasma glucose	≥126 mg/dL	100–125 mg/dL or treated to goal	<100 mg/dL

The guidelines for ideal total cholesterol, blood pressure, and fasting glucose are in agreement with the definitions used by the Third Adult Treatment Panel of the National Cholesterol Education Program (96), the Seventh Joint National Committee of the National Blood Pressure Education Program (97), and the American Diabetes Association (98), respectively.

Longitudinal cohort studies have reported that hypertension, dyslipidemia, and obesity are common co-morbidities in SLE, afflicting 30-60% of patients (99-101). Maternal cardiovascular health at conception and during the beginning of pregnancy has implications for the *in utero* environment. Obesity at time of conception can lead to alterations in metabolic adjustments during gestation, which can affect placental, embryonic and fetal growth. Increased body fat is associated with increased levels of

proinflammatory proteins, and obese women are more likely to enter pregnancy in a state of subclinical inflammation than non-obese women (102-104). Maternal obesity increases the risk of delivering an infant who is macrosomic (>4000 g) or large for gestational age (105-107).

Studies have shown that hypertension is a risk factor for preterm birth (108, 109), even in studies where pregnancies affected by preeclampsia were removed from the study population, with one study noting the risk of preterm birth increased 29% for each 10 mm Hg increase in diastolic blood pressure (110). Additionally, chronic hypertension is associated with fetal growth restriction and low birth weight (108, 109, 111), with the risk of preterm small for gestational age births being 5.5 times greater than in woman without hypertension and the risk of term small for gestational age births being 1.5-1.7 times greater than in women without hypertension (109).

Previous research, although limited, has demonstrated that increased total cholesterol during the first trimester is associated with preterm birth, and it has also been suggested that the association of cholesterol and preterm birth may be modified by maternal inflammation (110, 112, 113). One study reported the risk of preterm birth at <34 weeks to be 2.8 times greater among women with hypercholesterolemia than women with normal cholesterol (112), and another study estimated a 24% increase in the risk of preterm birth for each 40 mg/dL increase in cholesterol (110).

It has been theorized that maternal risk factors for cardiovascular disease may also be risk factors for fetal growth restriction and fetal programming (114). As SLE is a chronic inflammatory disease, it will be important to study the way these cardiovascular health factors affect preterm birth and fetal growth during SLE pregnancies. Additionally, understanding how SLE specific components of the disease, such as disease activity and autoantibodies, may modify the association is important in improving the outcomes of infants born to mothers with SLE.

SLE Disease Activity during Pregnancy

SLE is characterized by fluctuations of disease activity, with periods of high disease activity (i.e., flares) followed by periods of low disease activity. Disease indices have been designed and validated to describe the severity of a patient's disease activity, including the SELENA revision of the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) (115-118), British Isles Lupus Assessment Group

(BILAG) index (119, 120), Systemic Lupus Activity Measure (SLAM) Index (121, 122) and European Consensus Lupus Activity Measurement (ECLAM) index (123-125).

The effect of pregnancy on disease activity and flares in SLE has long been debated. Previous research has found that between 19 and 68% of women with SLE experience a flare during pregnancy (7, 39, 50-53, 57, 126-129). Risk factors for flare during pregnancy include active disease at conception, prednisone use, kidney disease and previous flares (52, 53, 57).

When compared to SLE patients who are not pregnant, there are conflicting results about the effect pregnancy has on disease activity (Table 6). Some studies report an increased rate of flares during pregnancy, while others report no difference in disease activity during pregnancy or post-partum. The rate of flares per person-months in pregnancy ranges from 0.06 – 0.14, compared to 0.04 – 0.05 in non-pregnant SLE patients (126, 127, 130, 131). A study by Lockshin et al. (132) analyzed flare characteristics of pregnant and non-pregnant SLE patients, including laboratory values (urine protein, anti-dsDNA, complement, hemoglobin, etc.) and symptoms (rash, fever, serositis, arthritis, neurologic events, etc.), and did not find a difference between women who were pregnant and women who were not (Table 5).

Table 5. Incidence of flares in SLE pregnancy per person-month

Reference	Country	Pregnancies (n)	Rate of Flares per Person-Month
Garsenstein 1962 (130)	US	33	32 weeks pre-pregnancy: 0.04 0-20 weeks of pregnancy: 0.13 21-40 weeks of pregnancy: 0.07 0-8 weeks postpartum: 0.27 9-40 weeks postpartum: 0.04
Mintz 1986 (130)	Mexico	102	Pregnant patients: 0.06 Non-pregnant patients: 0.04
Petri 1991 (126)	US	40	During pregnancy: 0.14 Post-partum: 0.05 Non-pregnant patients: 0.05
Ruiz-Irastorza 1996 (127)	UK	78	Pregnant patients (any time): 0.08 1st trimester: 0.008 2nd trimester: 0.15 3rd trimester: 0.07 1-year postpartum: 0.15 Non-pregnant patients: 0.04
Wong 1991 (131)	China	29	Pregnant patients: 0.08 Non-pregnant patients: 0.04

A limitation of the current literature is the inconsistency in which flares are defined. A different scale or set of parameters are used for each study, making it difficult to make comparisons across

studies. Many previous studies were also limited by a small sample size, which reduced power to determine differences in the rate of flares between pregnant and non-pregnant patients. Additionally, it can be challenging to differentiate between pregnancy related changes and changes that are related to SLE flares. Lateef et al. (37) constructed a comparison of pregnancy-related changes and flare characteristics to assist in distinguishing between the signs and symptoms of these two conditions (Table 6).

Table 6. Differentiating pregnancy-related changes from SLE flares during pregnancy (37).

Characteristic	Pregnancy-related changes	SLE flare
Mucocutaneous	Facial flush Palmar erythema Postpartum hair loss	Photosensitive rash Oral or nasal ulcers
Musculoskeletal	Arthralgias Myalgias	Inflammatory arthritis
Hematologic	Mild anemia Mild thrombocytopenia	Leucopenia, lymphopenia Immune hemolytic anemia Thrombocytopenia
Kidney	Physiologic proteinuria <300 mg/day	Active urinary sediment Proteinuria >300 mg/day
Immunologic	Higher complement levels	Falling complement levels Rising anti DNA levels
Others	Fatigue Mild edema Mild resting dyspnea	Fever Lymphadenopathy Pleuritis

From Lateef A, Petri M. Managing lupus patients during pregnancy. Best Practice & Research Clinical Rheumatology 2013;27(3):435-47 (37).

Research Gaps

Although pregnancy outcomes to women with SLE have improved in recent years, the prevalence of preterm birth and infants born small for gestational age remain two- to six-times greater in women with SLE, as compared to women in the general population (65). Many well-researched aspects of pregnancy in the general, “healthy” population remain unstudied in the population of women with SLE, and there are gaps in the literature relating to risk factors for poor pregnancy outcomes in SLE and the effect on pregnancy on the SLE disease course.

One aspect of pregnancy that has yet to be studied in a population of women with SLE is gestational weight gain (GWG). In 2009, the Institute of Medicine (IOM) formed a committee to update the recommendations for GWG. Guidelines were updated to reflect the recognized need for weight gain

recommendations to be specific to a woman's pre-pregnancy body mass index (BMI) and co-morbidities. Although the 2009 committee was not intended to develop GWG guidelines for specific diseases or conditions, a noticeable gap in the literature was the availability of data on the weight gain patterns in patients with autoimmune diseases, namely SLE. It is not presently known if women with SLE are gaining the appropriate amount of weight and what factors may affect weight gain in these women. Additionally, it has yet to be determined if the IOM guidelines for weight gain in the general population are appropriate for women with SLE.

The impact preconceptional cardiovascular health has on the occurrence of poor pregnancy outcomes in women with SLE is presently unknown. The American Heart Association (AHA)'s 2020 Impact Goals included the development of the concept of "ideal cardiovascular health," which focuses on primordial prevention and is composed of seven modifiable cardiovascular metrics: health factors (glucose, cholesterol, and blood pressure) and health behaviors (body mass index, physical activity, diet, and cigarette smoking) (95). Longitudinal cohort studies have reported that hypertension, dyslipidemia, and obesity are common in SLE, afflicting 30-60% of patients (99-101). Maternal cardiovascular health at conception and during the beginning of pregnancy has implications for the *in utero* environment, with obesity, hypertension and increased total cholesterol being associated with an increased risk of preterm birth and small for gestational age infants (108-113). As SLE is a chronic inflammatory disease, it will be important to study the way these cardiovascular health factors affect preterm birth and fetal growth during SLE pregnancies. Additionally, understanding how SLE specific components of the disease, such as disease activity and autoantibodies, may modify the association is important in improving the outcomes of infants born to mothers with SLE.

Finally, the impact of pregnancy on the disease course in women with SLE remains debated in the literature. Studies to date have focused on the change in disease activity for women during their pregnancy, without expanding the study period for their research questions much beyond the pregnancy itself. It remains unknown what impact pregnancy can have on metabolic changes, kidney involvement or overall disease activity (as defined by a validated disease activity indices, such as SELENA SLEDAI (Systemic Lupus Erythematosus Disease Activity Index) or the Physician's Global Assessment of disease activity (PGA)).

This dissertation addressed several of the gaps in the literature relating to pregnancy in women with SLE and determined:

1. if women with SLE are meeting the recommended Institute of Medicine guidelines for gestational weight gain,
2. factors associated with not meeting or exceeding gestational weight gain guidelines in SLE,
3. the proportion of women with SLE meeting the American Heart Association's classification of cardiovascular health in a cohort of pregnant SLE patients,
4. the effects of poor and intermediate cardiovascular health on pregnancy outcomes in SLE, and
5. the impact of pregnancy on the disease course of SLE.

CHAPTER 3: METHODS

Study Population

The Hopkins Lupus Pregnancy Cohort is a subset of the Hopkins Lupus Cohort, which has prospectively followed patients with SLE since 1987, with data available through February 6, 2015. Patients meeting the ACR or SLICC criteria for SLE (12, 13, 133) were eligible for enrollment in the cohort following informed consent. Patients enrolled in the Hopkins Lupus Cohort and SLE patients seen in the Hopkins Obstetrics Clinics were automatically referred to the Hopkins Lupus Pregnancy Cohort. Outside of Johns Hopkins Hospital, local patients were referred by their local rheumatologists, the Maryland Lupus Foundation, and self-referral (126). Patients who were not pregnant were seen on a quarterly basis at the Lupus Center in Baltimore, Maryland by a single rheumatologist.

Pregnant women were seen every on average every 4-6 weeks throughout their pregnancy. At the first clinic visit, patients were given a full medical examination and self-reported their obstetrical history, including previous abortions (spontaneous and elective) and previous deliveries. During each subsequent visit, a patient's weight was recorded, lupus disease activity was measured, medications were updated and laboratory tests were conducted. Laboratory tests included complete blood count (complement levels, autoantibodies, cholesterol and glucose) and urinalysis. Pregnancy outcome data were collected from women at the first postpartum visit to the Lupus Clinic or by telephone or email if a woman did not continue her medical care at the Lupus Clinic. Multiple pregnancies per patient were allowed in the analysis.

Data Collection and Measurement

Data collected in the Hopkins Lupus Pregnancy Cohort included pregnancy complications (intrauterine growth restriction, premature rupture of membranes, preeclampsia, pregnancy induced hypertension, gestational diabetes) and pregnancy outcomes (spontaneous miscarriage, stillbirth, termination, live birth, birth weight, small for gestational age, and preterm birth). All additional data on co-

morbidities (hypertension, diabetes, proteinuria, lupus nephritis), laboratory tests, patient demographics, SLE disease history, SLE disease activity, and treatment history were collected in the larger Hopkins Lupus Cohort.

Exposure Classification

Specific Aim 1 was an exploratory analysis of adherence to gestational weight gain and correlates of adherence. There were no specific exposures of interest.

In Specific Aim 2, the exposure of interest was pre-conceptional cardiovascular health defined according to three of the American Heart Association (AHA)'s metrics, body mass index (BMI), total cholesterol, and blood pressure, using the following criteria: *BMI*: (1) poor health (obese): ≥30 kg/m^2; (2) intermediate health (overweight): 25-29.9 kg/m^2; (3) ideal health (underweight/normal weight): <25 kg/m^2; *total cholesterol*: (1) poor health: ≥240 mg/dL; (2) intermediate health: 200–239 mg/dL or treated to goal; (3) ideal health: <200 mg/dL without treatment; *blood pressure*: (1) poor health: systolic ≥140 or diastolic ≥90 mm Hg; (2) intermediate health: systolic 120–139 or diastolic 80–89 mm Hg or treated to goal; (3) ideal health: <120/<80 mm Hg without treatment. Each metric was coded as a categorical variable, with "ideal health" as the referent group. Due to small sample size, poor health and intermediate health were collapsed into one exposure category for total cholesterol and blood pressure, with ideal health remaining the referent group. Each metric was also analyzed as a continuous variable. BMI, total cholesterol, and blood pressure at the most recent clinic visit in the one-year prior to conception were used to classify patients' cardiovascular health. If a clinic visit prior to conception was unavailable, the first measurement taken during the first trimester served as a surrogate for preconception health.

In Specific Aim 3, exposure was classified as pregnancy (yes/no), 1-year postpartum period (yes/no), or non-pregnant/non-postpartum period (unexposed). The exposure variables were included as time-varying covariates, so as to include all observations for an individual (including, for example, pre-pregnancy observations on women who became pregnant between visits).

Outcome Classification

In Specific Aim 1, the outcome of interest was the proportion of women with SLE who met the 2009 IOM guidelines for GWG based on pre-pregnancy BMI. Pre-pregnancy weight was defined as the most recent weight recorded at a visit within 12 months prior to pregnancy or, if not available, in the first trimester. The final pregnancy weight was the weight recorded closest to birth in the third trimester. Observed weight gain was calculated as the difference in the first and final weight measurement. The estimated total weight gain was calculated to account for variations in the timing of the first and final weight: (observed weight gain / weeks of gestation between weight measurements) x 40 weeks. Estimated total weight gain was classified according to IOM guidelines based on a woman's pre-pregnancy BMI: underweight (<18.5 kg/m^2), normal weight (18.5-24.9 kg/m^2), overweight (25.0-29.9 kg/m^2), obese (≥30 kg/m^2). The guidelines recommend the following total weight gain during pregnancy (8):

- underweight: 12.5-18 kg
- normal weight: 11.5-16 kg
- overweight: 7-11.5 kg
- obese 5-9 kg.

Total weight gain below the recommendations was considered inadequate weight gain, and total weight above the recommendations was considered excessive weight gain.

In Specific Aim 2, pregnancy outcomes of interest included gestational age at birth and birth weight for gestational age z-score. Gestational age at birth was based on maternally reported last menstrual period date and date of delivery and categorized as preterm (<37 weeks) and term (≥37 weeks), as well as analyzed as a continuous variable. Birth weight for gestational age z-score was based on US population reference percentiles of birth weight for singleton infants, stratified by infant sex (134). Z-scores in Oken et al. 2003 were calculated based on the distribution of birth weights for all live births born 22 to 44 weeks gestation in the US, 1999-2000, with a potential range of -2.58 to 2.58. Birth weight for gestational age z-score was analyzed as a continuous variable, as well as categorized based on the

percentile of birth weight for gestational age: <10th percentile (small for gestational age; SGA) and >90th percentile (large for gestational age; LGA).

In Specific Aim 3, the outcome was time to disease flare (allowing for multiple flares), with a flare classified according to two disease activity indices. PGA is a disease activity index ranging from 0 to 3, with 0 being no activity and 3 being severe disease activity (135). SELENA SLEDAI is a weighted disease activity index for activity related to SLE present within the previous 10 days, with a score range of 0 to 105 (118). Flares during follow-up were classified as:

1. Change in PGA ≥1 from previous visit
2. Change in SELENA SLEDAI ≥4 from the previous visit.

Covariates

Maternal age: Maternal age at the time of conception was analyzed as a continuous variable and categorized as ≤30 and >30 years in descriptive analyses in Aim 1.

Race: Patient race was classified as black and non-black.

Maternal education: Maternal education was based on self-reported years of education and categorized as ≤12 years, 13-16 years, and >16 years.

Duration of SLE: Duration of SLE at the time of conception was analyzed as a continuous variable and categorized as ≤5 and >5 years.

Infant Delivery Date: In Aims 1 and 2, infant delivery date (categorized as prior to January 1999 or between January 1999-February 2015) was considered a variable of interest due to changes in SLE prescribing patterns and general population shifts in BMI over time.

Medication Use during Pregnancy: Medication use during pregnancy was classified as (1) yes or (0) no for the following medications: anti-malarial, immunosuppressants, and prednisone. High-dose prednisone use was further classified as prednisone ≥15 mg/day during pregnancy. In Aim 3, prednisone and anti-malarial (hydroxychloroquine) use were analyzed as time-varying covariates.

High Disease Activity: Disease activity during pregnancy was classified according to the Physician Global Assessment of disease activity (PGA) index, with a score of >2 considered high disease activity.

Organ System Damage: Organ system damage at conception was classified according to the Systemic Lupus International Collaborating Clinics/American College of Rheumatology (SLICC/ACR) Damage Index (SDI), with a score of ≥1 indicating any organ system damage.

Renal Involvement: Renal involvement during pregnancy was defined as renal Lupus Activity Index score >1 at any time during pregnancy.

Autoantibodies during Pregnancy: Autoantibodies during pregnancy included the presence of any of the following: low complement 3 (C3), low complement 4 (C4), and anti-double stranded DNA (anti-dsDNA; ever positive).

Elevated Serum Creatinine: Elevated serum creatinine during pregnancy was defined as serum creatinine ever >1 mg/dl.

Study Analysis Plan

Specific Aim 1: To estimate the proportion of pregnant women with systemic lupus erythematosus (SLE) who meet the Institute of Medicine (IOM) guidelines for gestational weight gain (GWG) and to determine factors associated with adherence to IOM guidelines for GWG.

***Sub-Aim 1A*: To estimate gestational weight gain trajectories for women with SLE.**

Adherence to the IOM recommendations was classified as a categorical variable (inadequate, adequate or excessive weight gain) based on pre-pregnancy BMI. An exploratory analysis determined factors associated with not meeting IOM guidelines by Fisher's exact test of differences in proportions and ANOVA compared differences in means. A generalized logit model analysis with stepwise selection determined predictors of inadequate and excessive weight gain, both compared to adequate weight gain. Generalized estimating equation methods were used to account for the potential correlation of multiple pregnancies per patient being included in the analysis (136). Potential variables were entered into the model if α was <0.2 and remained in the model if α was <0.05. Weight trajectories for gestational weight gain were estimated using mixed models. Mixed models include fixed and random effects and are ideal for repeated measures with varying number of measurements and time between measurements per subject (137). The model included a random effect for the intercept and for time (weeks of gestation). The

fixed effects included a linear effect for time, quadratic effect for time, BMI group, and interaction for BMI group and time.

Specific Aim 2: To estimate the effect of preconceptional cardiovascular health, as measured by blood pressure, total cholesterol and body mass index, on preterm birth and fetal growth (birth weight for gestational age z-score) in women with SLE.

Unadjusted differences in the prevalence of preterm birth, SGA, and LGA among live births by pre-conceptional cardiovascular health were analyzed descriptively by Fischer's exact test. Differences in mean gestational age and mean birth weight for gestational age z-score by pre-conceptional cardiovascular health were analyzed by ANOVA. Multivariable logistic regression models estimated odds ratios (OR) and 95% confidence intervals for the association of each maternal cardiovascular health factor and categorical pregnancy outcomes of interest (preterm birth, SGA, and LGA). Multivariable linear regression models estimated associations of each maternal cardiovascular health factor with continuous outcome measures (gestational age at birth and birth weight for gestational age z-score). To account for the correlation between outcomes that would occur from patients contributing more than one pregnancy to this analysis, generalized estimating equations (GEE) with an exchangeable correlation structure were used (136). Confounders were assessed based on combined directed acyclic graph (DAG) minimally sufficient set that was reduced based on a 10% change in beta (β) estimates. Models with BMI as the exposure were adjusted for prednisone use during pregnancy and patient race, and blood pressure models were adjusted for renal involvement during pregnancy and patient race. For the exposure of total cholesterol, three adjusted models were estimated: 1) adjusted for patient race and prednisone use during pregnancy; 2) adjusted for patient race and anti-malarial use during pregnancy; and 3) adjusted for patient race, prednisone use during pregnancy, and anti-malarial use during pregnancy.

Specific Aim 3: To estimate the effect of pregnancy on disease activity (i.e., disease flares) in SLE using a Cox proportional hazards model.

***Sub-Aim 3a*: To compare traditional methods for estimating the incidence of disease flares to the estimates from counting process and stratified Cox proportional hazards models.**

***Sub-Aim 3b*: To perform a sensitivity analysis excluding women without a pregnancy from the study population.**

All women with SLE in the Hopkins Lupus Cohort between the ages of 15 and 45 were included in the analysis for Specific Aim 3, regardless of pregnancy status. Women with only one measurement of disease activity were excluded as time to event could not be determined for these women. The time of entry into the Hopkins Lupus Cohort was considered the initial measurement for all women. Patients were right censored and removed from the risk set at age 45 (end of reproductive years), menopause (if prior to age 45 years), death, loss to follow-up, or February 6, 2015, the end of follow-up. If patients had a gap of more than one year in study visits, patients were considered lost to follow-up, but were allowed to re-enter the cohort when study visits resumed. The time between when a patient exited and re-entered the cohort did not contribute to person-time at risk.

Crude incidence rates were calculated as the observed number of flares / total person-time for each exposure period. Incidence rate ratios and corresponding 95% confidence intervals were calculated for pregnancy vs. unexposed periods and postpartum vs. unexposed periods. The analysis used two separate variations of Cox models to estimate the hazard rate ratio of flares in pregnancy and postpartum periods compared to unexposed periods: the standard counting process Cox proportional hazards model and the stratified Cox model. The counting process Cox proportional hazards model accounted for repeated measures, but did not take into account the order in which events occur. In the stratified Cox model, a stratum for the time interval number was included in the model so a patient was not at risk for a second flare without having experienced a previous flare.

If a woman had more than one pregnancy, all pregnancies (as well as postpartum periods) were included in the analysis. Due to repeated events of flares being counted in the same patient and patients being allowed to exit and re-enter the analytic cohort, 95% confidence intervals were estimated with 1,000 bootstrap replications sampled with replacement (138). Using the same model, hazard ratios were calculated between 1) pregnant and unexposed periods and 2) postpartum and unexposed periods. To account for the time-varying exposures, a new patient ID was created for each patient which changed when the exposure changed, and both the original ID and new ID were included in the Cox models.

In order to determine if all women in the Hopkins Lupus Cohort were an appropriate comparator group for women who became pregnant, two sensitivity analyses were performed. The first included only women who had a history of pregnancy or had an observed pregnancy while in the Hopkins Lupus Cohort. The second sensitivity analysis included only women who had an observed pregnancy while in the Hopkins Lupus Cohort. All analyses were conducted in SAS 9.3 (Cary, North Carolina).

CHAPTER 4: GESTATIONAL WEIGHT GAIN IN PREGNANT WOMEN WITH SYSTEMIC LUPUS ERYTHEMATOSUS

Background

In 1990, the Institute of Medicine (IOM) published guidelines for ideal weight gain during pregnancy based on pre-pregnancy BMI. These guidelines were updated in 2009 due in part, to the concern of rising obesity rates in the population (8). Although the 2009 committee was not intended to develop gestational weight gain (GWG) guidelines for specific diseases or conditions, a noticeable gap in the literature was the availability of data on the weight gain patterns in patients with autoimmune diseases. Of particular interest was systemic lupus erythematosus (SLE), a disorder that largely affects women between the ages of 15 and 44 (1). It is not presently known if women with SLE are gaining the appropriate amount of weight and what factors may affect weight gain in these women.

Gestational weight gain is the amount of weight a mother gains throughout her pregnancy and is composed of maternal and fetal products of conception. The average weight gain attributable to fetal components is 4.8 kilograms, comprised of the fetus (~3.3 kilograms), the placenta (~0.7 kilograms) and amniotic fluid (~0.8 kilograms). For maternal components, the average weight gained is 7 kilograms, largely due to increase in fat (~4.0 kilograms), blood volume (~1.2 kilograms) and extracellular fluid (~1.2 kilograms) (69). The pattern of weight gain during pregnancy varies greatly among women. One study found the average weekly weight gain for the second and third trimesters was higher for underweight and normal weight women, compared to overweight and obese women. Additionally, in this study, all women except obese women had higher weekly rates of weight gain in the second trimester than in the third trimester (72).

The appropriate amount of weight gained during pregnancy has great implications for the infant: gaining too much weight during pregnancy has been shown to be associated with delivering large for gestational age or macrosomic (>4000 g) infants (73-89), while insufficient weight gain is associated with the delivery of a small for gestational age infant (74, 75, 78-84, 90). Gestational weight gain also has implications for preterm birth. There appears to be a U-shaped association of GWG with preterm birth,

with modification by pre-pregnancy BMI (10, 91-94). Among women who are underweight according to their pre-pregnancy BMI, insufficient GWG is associated with an increased risk of preterm birth, and this association weakens as pre-pregnancy BMI increases. Excessive GWG may be associated with preterm birth in women of all pre-pregnancy BMI categories (9, 10). Gestational weight gain also has implications throughout childhood, with excessive weight gain being associated with childhood obesity (94, 139, 140).

The vast majority of women in the general population do not meet the IOM guidelines for weight gain, with one study finding that 17% of mothers had inadequate, 31% had adequate, and 53% had excessive weight gain (11). Women classified as overweight or obese are at increased risk of gaining more than the recommended amount of weight during pregnancy, compared to women with normal BMI. Unfortunately, the proportion of women who are exceeding the guidelines for GWG is increasing (11), which is why the IOM committee has called for a paradigm shift in how preconception and prenatal advice concerning weight gain is being delivered to women of childbearing ages. The objectives of this study were to estimate the proportion of women with SLE who meet the IOM guidelines for GWG and to determine correlates of adherence to IOM guidelines for GWG.

Methods

Study population

The Hopkins Lupus Pregnancy Cohort is a subset of the Hopkins Lupus Cohort, which has prospectively followed patients with SLE since 1987, with data available through February 6, 2015 (n=515). Patients meeting the American College of Rheumatology (ACR) or Systemic Lupus International Collaborating Clinics (SLICC) criteria for SLE (12, 13, 133) were eligible for enrollment in the cohort following informed consent. Patients enrolled in the Hopkins Lupus Cohort and SLE patients seen in the Hopkins Obstetrics Clinics were automatically referred to the Hopkins Lupus Pregnancy Cohort. Outside of Johns Hopkins Hospital, local patients were referred by their local rheumatologists, the Maryland Lupus Foundation and self-referral (126). Pregnant women were seen every 4-6 weeks throughout their pregnancy at the Lupus Center in Baltimore, Maryland by a single rheumatologist (average 5.3 weeks). During each visit, a patient's weight was recorded, lupus disease activity was determined by the physician global assessment of disease activity (PGA), medications were updated and laboratory tests were

conducted. Laboratory tests included complete blood count, complement levels, autoantibodies and urinalysis.

Gestational weight gain

The outcome of interest was the proportion of women with SLE who met the 2009 IOM guidelines for GWG based on pre-pregnancy BMI. Pre-pregnancy weight was defined as the most recent weight recorded at a visit within 12 months prior to pregnancy (average weeks prior to pregnancy: 8.4 weeks, SD: 1.9) or, if not available in the first trimester (n=64, average gestational age: 8.4 weeks, SD: 3.2). The final pregnancy weight was the weight recorded closest to birth in the third trimester (average gestational age: 34.8 weeks, SD: 2.9). Observed weight gain was calculated as the difference in the first and final weight measurement. The estimated total weight gain was calculated to account for variations in the timing of the first and final weight: (observed weight gain / weeks of gestation between weight measurements) x 40 weeks.

Estimated total weight gain was classified according to IOM guidelines based on a woman's pre-pregnancy BMI: underweight (<18.5 kg/m^2), normal weight (18.5-24.9 kg/m^2), overweight (25.0-29.9 kg/m^2), obese (≥30 kg/m^2). The guidelines recommend the following total weight gain during pregnancy (8):

- underweight: 12.5-18 kg
- normal weight: 11.5-16 kg
- overweight: 7-11.5 kg
- obese 5-9 kg.

Total weight gain below the recommendations was considered inadequate weight gain, and total weight above the recommendations was considered excessive weight gain.

Covariates

Population characteristics of interest included self-reported race (black vs. non-black), education, age at conception and duration of SLE. Infant birth date (categorized as prior to January 1999 or between January 1999 and February 2015) was considered a variable of interest due to changes in SLE

prescribing patterns and general population shifts in BMI over time. Information on medication SLE treatment used during pregnancy included: anti-malarial, immunosuppressants, prednisone, and prednisone ≥15 mg/day. Clinical characteristics and biomarkers of SLE recorded as ever occurring during pregnancy were: renal involvement (renal Lupus Activity Index >1), elevated serum creatinine (>1 mg/dl), high Physician Global Assessment (PGA ≥2), low complement (C3 and C4), and anti-dsDNA (ever positive). Maternal cumulative organ system damage at conception was measured by the SLICC/American College of Rheumatology Index (SDI), with a score of ≥1 representing the presence of any organ system damage. Pre-pregnancy blood pressure on the study visit closest to conception in the one-year prior to pregnancy or 1st trimester was classified according to American Heart Association (AHA) criteria for cardiovascular health: poor/intermediate blood pressure: systolic ≥120 or diastolic ≥80 mm Hg or treated to goal; ideal health: <120 and <80 mm Hg without treatment (95). Pre-pregnancy cholesterol on the study visit closest to conception in the one-year prior to pregnancy or 1st trimester was classified according to AHA criteria for cardiovascular health: poor/intermediate cholesterol: ≥200 mg/dL or treated to goal; ideal health: <200mg/dL without treatment (95).

Pregnancy outcomes of interest included gestational age at birth and birth weight for gestational age z-score. Gestational age at birth was based on maternally reported last menstrual period date and date of delivery and categorized as preterm (<37 weeks) and term (≥37 weeks), as well as analyzed as a continuous variable. Birth weight for gestational age z-score was based on US population reference percentiles of birth weight for singleton infants, stratified by infant sex (134). Z-scores in Oken et al. 2003 were calculated based on the distribution of birth weights for all live births born 22 to 44 weeks gestation in the US, 1999-2000, with a potential range of -2.58 to 2.58. Birth weight for gestational age z-score was analyzed as a continuous variable, as well as categorized based on the percentile of birth weight for gestational age: <10th percentile (small for gestational age; SGA) and >90th percentile (large for gestational age; LGA).

Subject selection

During the study period, there were 515 pregnancies in the Hopkins Lupus Cohort, of which 431 were live births (Figure 1). More than one singleton live birth per patient was allowed in the analysis.

Pregnancies without a weight measurement in the one year prior to the last menstrual period pre-pregnancy or during the first trimester, and/or without a weight measurement in the third trimester, were excluded. Of the 421 singleton live births, 291 pregnancies had a weight measurement during the one year prior to pregnancy or during the first trimester, and of these, 211 pregnancies had an additional weight measurement during the third trimester. Live births excluded from the analysis (210 of 421 singleton live births) were more frequently to mothers with a high school education and a pregnancy outcome date prior to 1999. Additionally, excluded births were to mothers with a lower frequency of anti-malarial use during pregnancy and shorter disease duration.

Analysis

Adherence to the IOM recommendations was classified as a categorical variable (inadequate, adequate, or excessive weight gain) based on pre-pregnancy BMI. The percent of women who had inadequate, adequate, or excessive weight gain, based on their pre-pregnancy BMI group, was estimated, and the mean estimated total weight gain was calculated. An exploratory analysis determined factors associated with not meeting IOM guidelines by Fisher's exact test of differences in proportions and ANOVA compared differences in means. A generalized logit model analysis with stepwise selection determined predictors of inadequate and excessive weight gain, both compared to adequate weight gain. Generalized estimating equation methods were used to account for the potential correlation of multiple pregnancies per patient being included in the analysis (136). Potential variables were entered into the model if α was <0.2 and remained in the model if α was <0.05. Covariates included in model were race, education, infant delivery year, age at conception, duration of SLE, medication use ever during pregnancy (anti-malarial, immunosuppressants, prednisone, and prednisone ≥15 mg/day), SDI at conception and clinical characteristics ever occurring during pregnancy (renal involvement, elevated serum creatinine, high PGA, low complement, and anti-dsDNA).

Weight trajectories for gestational weight gain were estimated using mixed models. Mixed models include fixed and random effects and are ideal for repeated measures with varying number of measurements and time between measurements per subject. The model included a random effect for the intercept and for time (weeks of gestation). The fixed effects included a linear effect for time, quadratic

effect for time, BMI group, and interaction for BMI group and time. All analyses were conducted with SAS 9.3 (Cary, North Carolina).

Results

There were 211 pregnancies among 182 women included in the analysis. The majority of pregnancies were to women who were white (59%), with a median age at pregnancy of 30 years and median disease duration of 5 years. Overall, 34% of pregnancies had inadequate weight gain, 24% had adequate weight gain, and 42% had excessive weight gain (Figure 2). Differences were observed by pre-pregnancy BMI. Among underweight women, 67% of pregnancies had inadequate GWG, and 33% had adequate GWG. Among normal weight women, pregnancies were fairly evenly divided, with 30%, 32%, and 38% having inadequate, adequate, and excessive weight gain, respectively. On the other hand, among overweight and obese women, few had inadequate GWG, 51% of both groups had excessive GWG, and only 19% and 7% of overweight and obese women, respectively, gained within the recommended guidelines. There were nine pregnancies in which the mother lost weight, ranging from 1.5 kg to 16.0 kg; all had BMI in the range of overweight or obese. The mean (SD) estimated total weight gain was 10.9 (3.4) kg for underweight women, 14.7 (6.4) for normal weight women, 12.9 (8.8) for overweight women, and 8.3 (12.4) for obese women.

In exploratory analyses, there were observed differences in adherence to IOM guidelines by race, elevated creatinine during pregnancy, pre-pregnancy blood pressure, and pre-pregnancy BMI (Table 7). The mean pre-pregnancy BMI for patients with inadequate, adequate, and excessive weight gain was 26.9 kg, 23.4 kg, and 26.6 kg, respectively (p=0.004). Of interest, there were no differences in weight gain adherence to IOM guidelines by SLE medication use during pregnancy, and adherence to GWG guidelines did not appear to correlate with pregnancy outcomes.

In exploratory analyses, no differences in guideline adherence were observed for infants who were small for gestational age (SGA) compared to infants who were not SGA (p=0.2), for infants who were large for gestational age (LGA) compared to infants who were not LGA (p=0.8), or for infants who were preterm compared to term (p=0.6). The mean gestational age at birth (p=0.2) and birthweight percentile (p=0.07) were both similar across categories of guideline adherence.

In logistic regression models, stepwise selection determined continuous pre-pregnancy BMI and maternal education level were predictors of inadequate and excessive weight gain (Table 8). With each 1 kg/m^2 increase in pre-pregnancy BMI, the odds of inadequate weight gain and excessive weight gain both increased 12%. Compared to patients with a greater than college education, patients with a high school education had approximately three times the odds of inadequate weight gain and twice the odds of excessive weight gain.

Figure 3 illustrates the mean predicted change in maternal weight, stratified by pre-pregnancy BMI category (underweight/normal weight, overweight, and obese). Normal weight and underweight women were pooled into one category due to the small number of underweight women. The weight gain trajectory did not change in a sensitivity analysis removing underweight women from the analytic cohort. The weight gain trajectories in normal weight/underweight women and overweight women appear to be similar, with weight increasing steadily throughout pregnancy. The trajectories for obese women, however, were different from normal weight/underweight and overweight women, with a decrease in weight observed at the beginning of pregnancy.

Discussion

In this study of pregnant women with SLE, 34% of pregnancies had inadequate weight gain, 24% of pregnancies had adequate weight gain, and 42% had excessive weight gain, rates similar to those observed in the general population of pregnant women in the United States (141). In a recent analysis of the Pregnancy Risk Assessment Monitoring System (PRAMS) 2010-2011, 21%, 32%, and 47% of women reported having inadequate weight gain, adequate weight gain, and excessive weight gain during pregnancy, respectively (141). In PRAMS, underweight women and normal weight women had decreased odds of excessive weight gain, while overweight and obese women had increased odds of excessive weight gain (141, 142). Similar patterns were observed in our cohort of SLE women, with the frequency of excessive weight gain lower in normal weight and underweight women than in overweight and obese women.

In exploratory analyses, some demographic and clinical characteristics were found to be associated with gestational weight gain, but in adjusted models, only pre-pregnancy BMI and maternal education were found to predict gestational weight gain. The demographic differences observed in our

study, increased frequency of inadequate weight gain among black patients compared to non-black patients, and increased frequency of inadequate weight gain among patients with a high school education compared to more than a college education, have also been reported in the general population (141).

In the general population, a previous study has reported that among normal weight women, there is an increased odds of excessive weight gain in patients with hypertensive conditions (141). In our exploratory analysis, we also observed differences by pre-pregnancy blood pressure, with an increased frequency of both inadequate and excessive weight gain among patients with intermediate and poor pre-pregnancy blood pressure compared to patients with ideal pre-pregnancy blood pressure.

A difference was observed in exploratory analyses in IOM guideline adherence for patients who had elevated creatinine during pregnancy compared to patients who did not. Although the number of patients with elevated creatinine was small (n=15), 53% of these patients had inadequate weight gain compared to 33% of patients without elevated creatinine, and 0% had adequate weight gain, compared to 26% of patients without elevated creatinine. Elevated creatinine indicates renal insufficiency (143). While we did not observe any differences in guideline adherence for patients with and without renal involvement during pregnancy, it appears that patients with elevated creatinine during pregnancy are at particular risk for not adhering to recommended guidelines, which may warrant further investigation.

Of particular interest was the lack of association of SLE medication use during pregnancy and gestational weight gain in exploratory analyses, including prednisone use or use of high prednisone dose (≥15 mg/day). This is in contrast to what was expected, given that prednisone has been found to increase adipose tissue among users (144). Only 21 of the 102 pregnancies with maternal exposure to prednisone initiated prednisone treatment during pregnancy. It may be that no increased frequency of excessive gestational weight gain with prednisone use was observed because patients have already experienced the increase in body mass associated with prednisone use, and no additional weight increase occured during pregnancy.

Results from weight gain trajectory analyses suggest that the change in weight throughout pregnancy is similar for underweight, normal weight, and overweight women, but varies for obese women. Among obese women, weight appears to decrease during the 1st trimester and then increase at the start of the 2nd trimester. This is of interest, as weight measurements for women in this study were based on

clinic measurements rather than self-report. Therefore, the weight fluctuations suggest a true initial decrease in weight and variability in weight gain among obese women, rather than an observed bias due to inaccurate reporting pre-pregnancy weight that may occur with self-reported weights.

Previous research has found that factors associated with non-adherence, such as race, education and certain co-morbidities vary by BMI group (141). A limitation of the present analysis is that the sample size of 211 women did not provide sufficient power to analyze interactive effects of BMI with demographic and clinical factors. Such analyses of interactive effects may help provide additional clarity on the unexpected results of no difference in guideline adherence by maternal prednisone use during pregnancy, which we were unable to discern due to the limited sample size. Additionally, data were unavailable on patients' physical activity and diet, which may help further explain differences in weight gain patterns in this population. Our study was also limited by the lack of weight measurements for all live births in the cohort, which resulted in 210 pregnancies being excluded from the analysis. Demographic and clinical differences in patients included and excluded were observed, which could have implications for our results.

Despite these limitations, our study was strengthened by the prospective collection of clinically recorded weights, rather than relying on self-report of pre-pregnancy weight of total gestational weight gain by the patient, which has been found to often be inaccurately remembered at the time of delivery (145). Additionally, the present analysis benefits from weights being measured at multiple times during pregnancy, with a median of 4 visits per patient, which allowed for weight gain trajectories to be constructed. Although the sample size is modest, this study reports one of the largest cohorts of pregnant women with SLE, and it is the first study to analyze gestational weight gain patterns in SLE.

Conclusion

The results of this analysis show that the majority of women with SLE do not meet the IOM guidelines for gestational weight gain. Pre-pregnancy BMI was found to be associated with not meeting guidelines in this study population, which is similar to what is observed in the general population. Targeted interventions to increase patient awareness about GWG guidelines and improve BMI prior to women with SLE becoming pregnant are important next steps for rheumatologists and obstetricians

treating SLE patients to adopt in order to improve guideline adherence. Due to the observed association of education on adherence to GWG guidelines, it will be particularly important to focus interventions on the educational status of women. It has yet to be determined if the IOM guidelines for weight gain in the general population are appropriate for women with SLE, and future studies are necessary to determine if pregnancy outcomes in women with SLE are improved when IOM guidelines for gestational weight gain are met. As research in the general population has shown that adherence to IOM guidelines has significant implications for the future health of both the mother and infant, it is important to further understand what factors may be associated with non-adherence to guidelines in women with SLE. Physicians are encouraged to share the IOM physician toolbox for gestational weight gain (http://nationalacademies.org/hmd/activities/children/pregnancyweightdissemination/2013-sep-09/toolkit.aspx) with their patients in order to promote proper weight gain during pregnancy.

Table 7. Demographic and clinical factors associated with estimated total weight gain during pregnancy for women with SLE in the Hopkins Lupus Pregnancy Cohort (n=211)

	n	Inadequate n (%)	Adequate n (%)	Excessive n (%)	Fisher X^2 p-value
Race					
Non-Black	146	41 (28.1%)	39 (26.77%)	66 (45.2%)	0.02
Black	65	31 (47.7%)	12 (18.5%)	22 (33.9%)	
Age					
≤30	101	34 (33.7%)	26 (25.7%)	41 (40.6%)	0.9
>30	110	38 (34.6%)	25 (22.7%)	47 (42.7%)	
Education					
HS Education (≤12 years)	57	25 (43.9%)	9 (15.8%)	23 (40.4%)	0.2
College (13-16 years)	100	34 (34.0%)	24 (24.0%)	42 (42.0%)	
Greater than College (>16 years)	54	13 (24.1%)	18 (33.3%)	23 (42.6%)	
SLE Duration					
≤5 years	101	33 (32.7%)	23 (22.8%)	45 (44.6%)	0.7
>5 years	110	39 (35.4%)	28 (25.5%)	43 (39.1%)	
Prednisone Use During Pregnancy					
No	109	35 (32.1%)	29 (26.6%)	45 (41.3%)	0.7
Yes	102	37 (36.3%)	22 (21.6%)	43 (42.2%)	
Prednisone Use ≥15 mg/day During Pregnancy among Prednisone Users (n=102)					
No	54	18 (33.3%)	10 (18.5%)	26 (48.2%)	0.4
Yes	48	19 (39.6%)	12 (25.0%)	17 (35.4%)	
Anti-malarial Use During Pregnancy					
No	59	19 (32.2%)	12 (20.3%)	28 (47.5%)	0.5
Yes	152	53 (34.9%)	39 (25.7%)	60 (39.5%)	
Immunosuppressants Use During Pregnancy					
No	174	61 (35.1%)	44 (25.3%)	69 (39.7%)	0.5
Yes	37	11 (29.7%)	7 (18.9%)	19 (51.4%)	
Highest PGA During Pregnancy					
<2	175	61 (34.9%)	44 (25.1%)	70 (40.0%)	0.6
≥2	36	11 (30.6%)	7 (19.4%)	18 (50.0%)	
SDI at Conception					
0	132	41 (31.1%)	37 (28.0%)	54 (40.9%)	0.2
≥1	79	31 (39.2%)	14 (17.7%)	34 (43.0%)	
Renal Involvement During Pregnancy					
No	151	51 (33.8%)	38 (25.2%)	62 (41.1%)	0.9
Yes	60	21 (35.0%)	13 (21.7%)	26 (43.3%)	
Elevated Creatinine During Pregnancy					
No	196	64 (32.7%)	51 (26.0%)	81 (41.3%)	0.03
Yes	15	8 (53.3%)	0 (0.0%)	7 (46.7%)	
Low C3 During Pregnancy					
No	160	54 (33.8%)	33 (20.6%)	73 (45.6%)	0.06
Yes	51	18 (35.3%)	18 (33.3%)	15 (29.4%)	
Low C4 During Pregnancy					
No	135	45 (33.3%)	28 (20.7%)	62 (45.9%)	0.2
Yes	76	27 (35.5%)	23 (30.3%)	26 (34.2%)	
Anti-dsDNA+ During Pregnancy					
No	128	40 (31.3%)	33 (25.8%)	55 (43.0%)	0.5

Yes	83	32 (38.6%)	18 (21.7%)	33 (39.8%)	
Pre-Pregnancy Blood Pressure					
Ideal	105	31 (29.5%)	34 (32.4%)	40 (38.1%)	0.02
Intermediate/Poor	106	41 (38.7%)	17 (16.0%)	48 (45.3%)	
Pre-Pregnancy Cholesterol (n=200)					
Ideal	178	57 (32.0%)	44 (24.7%)	77 (43.3%)	0.9
Intermediate/Poor	22	5 (22.7%)	8 (36.4%)	9 (40.9%)	
Pre-Pregnancy BMI, kg/m^2					
Under weight (<18.5)	9	6 (66.7%)	3 (33.3%)	0 (0.0%)	0.001
Normal weight (18.5-24.9)	112	34 (30.4%)	36 (32.1%)	42 (37.5%)	
Overweight (25.0-29.9)	47	14 (29.8%)	9 (19.2%)	24 (51.1%)	
Obese (≥30)	43	18 (41.9%)	3 (7.0%)	22 (51.2%)	
Infant birth date					
January 1999 – February 2015	156	49 (31.4%)	39 (25.0%)	68 (43.6%)	0.4
Prior to January 1999	55	23 (41.8%)	12 (21.8%)	20 (36.4%)	
Small for gestational age (n=198)					
No	159	57 (35.9%)	32 (20.1%)	70 (44.0%)	0.2
Yes	39	12 (30.8%)	13 (33.3%)	14 (35.9%)	
Large for gestational age (n=198)					
No	190	67 (35.3%)	43 (22.6%)	80 (42.1%)	0.8
Yes	8	2 (25.0%)	2 (25.0%)	4 (50.0%)	
Preterm birth					
No	160	52 (32.5%)	41 (25.6%)	67 (41.9%)	0.6
Yes	51	20 (39.2%)	10 (19.6%)	21 (41.2%)	
Pregnancy induced hypertension (n=162)					
No	150	48 (32.0%)	32 (21.3%)	70 (46.7%)	0.3
Yes	12	6 (50.0%)	3 (25.0%)	3 (25.0%)	
Pre-eclampsia (n=166)					
No	151	48 (31.8%)	34 (22.5%)	69 (45.7%)	0.5
Yes	15	7 (46.7%)	2 (13.3%)	6 (40.0%)	
Caesarian section (n=166)					
No	103	39 (37.9%)	22 (31.4%)	42 (40.8%)	0.3
Yes	63	17 (27.9 %)	14 (22.2%)	32 (50.8%)	
Premature rupture of membranes (n=164)					
No	146	49 (33.6%)	32 (21.9%)	65 (44.5%)	0.9
Yes	18	5 (22.8%)	4 (22.2%)	9 (50.0%)	
		Mean (SD)	Mean (SD)	Mean (SD)	ANOVA p-value
Age at conception, years	211	30.3 (5.1)	30.5 (5.0)	30.0 (4.4)	0.8
Disease duration, years	211	6.5 (5.3)	7.4 (5.8)	6.2 (5.6)	0.5
Highest PGA during pregnancy	211	1.0 (0.7)	0.9 (0.7)	1.1 (0.7)	0.4
SDI at conception	211	0.9 (1.4)	0.4 (0.8)	0.8 (1.5)	0.2
Highest daily prednisone dose during pregnancy among prednisone users, mg	102	21.0 (17.1)	16.5 (12.7)	15.5 (13.3)	0.2
Pre-pregnancy BMI, kg/m^2	211	26.9 (7.4)	23.4 (4.4)	26.6 (5.7)	0.004
Gestational age at birth, weeks	211	37.1 (2.6)	37.6 (1.8)	37.6 (2.0)	0.2
Birth weight percentile	198	31.3 (23.8)	31.4 (26.6)	40.1 (27.1)	0.07
Birth weight z-score	198	-0.63 (0.84)	-0.65 (0.96)	-0.36 (0.97)	0.1

BMI: body mass index; HS: high school; PGA: physician global assessment of disease activity; SD: standard deviation; SDI: SLICC/ACR Damage Index; SLE: systemic lupus erythematosus

Table 8. Predictors of adherence to 2009 IOM guidelines for gestational weight gain[a] for women with SLE in the Hopkins Lupus Pregnancy Cohort (n=211).

	Inadequate	**Excessive**
	OR (95% CI)	OR (95% CI)
Education		
HS Education (≤12 years)	3.31 (1.12, 9.75)	1.74 (0.62, 4.90)
College (13-16 years)	2.05 (0.79, 5.32)	1.40 (0.63, 3.13)
Greater than College (>16 years)	1.0 (ref)	1.0 (ref)
Pre-pregnancy BMI, kg/m^2	1.12 (1.03, 1.22)	1.12 (1.03, 1.21)

[a]Stepwise selection: entered into model if $\alpha < 0.2$; remained in model if $\alpha < 0.05$

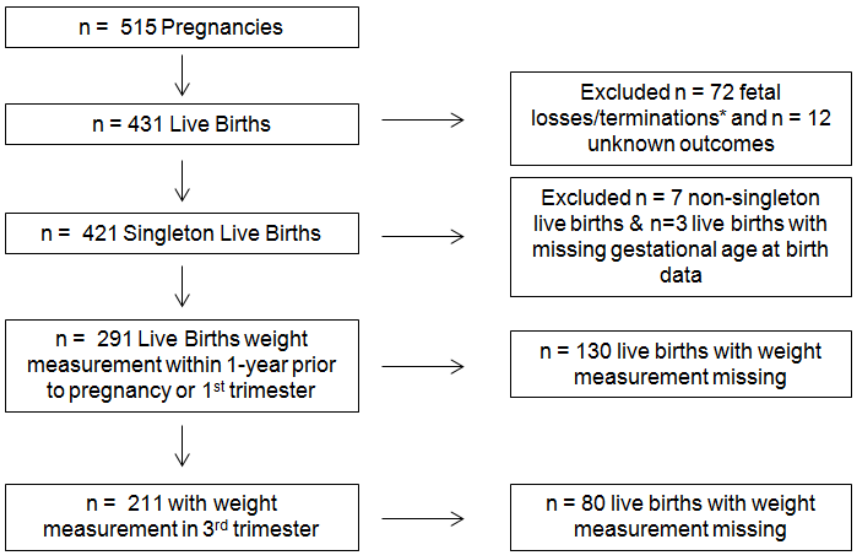


Figure 1. Study population for the Hopkins Lupus Pregnancy Cohort, 1987 to February 2015.

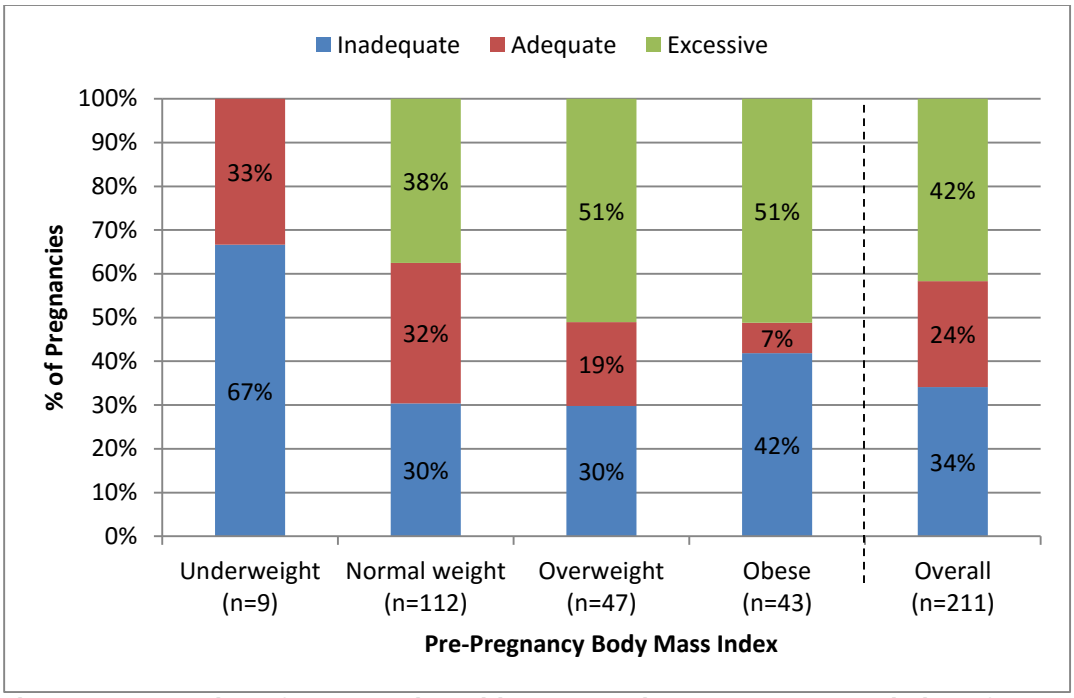


Figure 2. Proportion of pregnancies with SLE meeting IOM recommendations for gestational weight gain based on maternal pre-pregnancy body mass index[A] in the Hopkins Lupus Pregnancy Cohort (n=211).

[A]Pre-pregnancy body mass index classified as underweight (<18.5 kg/m^2), normal weight (18.5-24.9 kg/m^2), overweight (25.0-29.9 kg/m^2), and obese (≥30 kg/m^2)

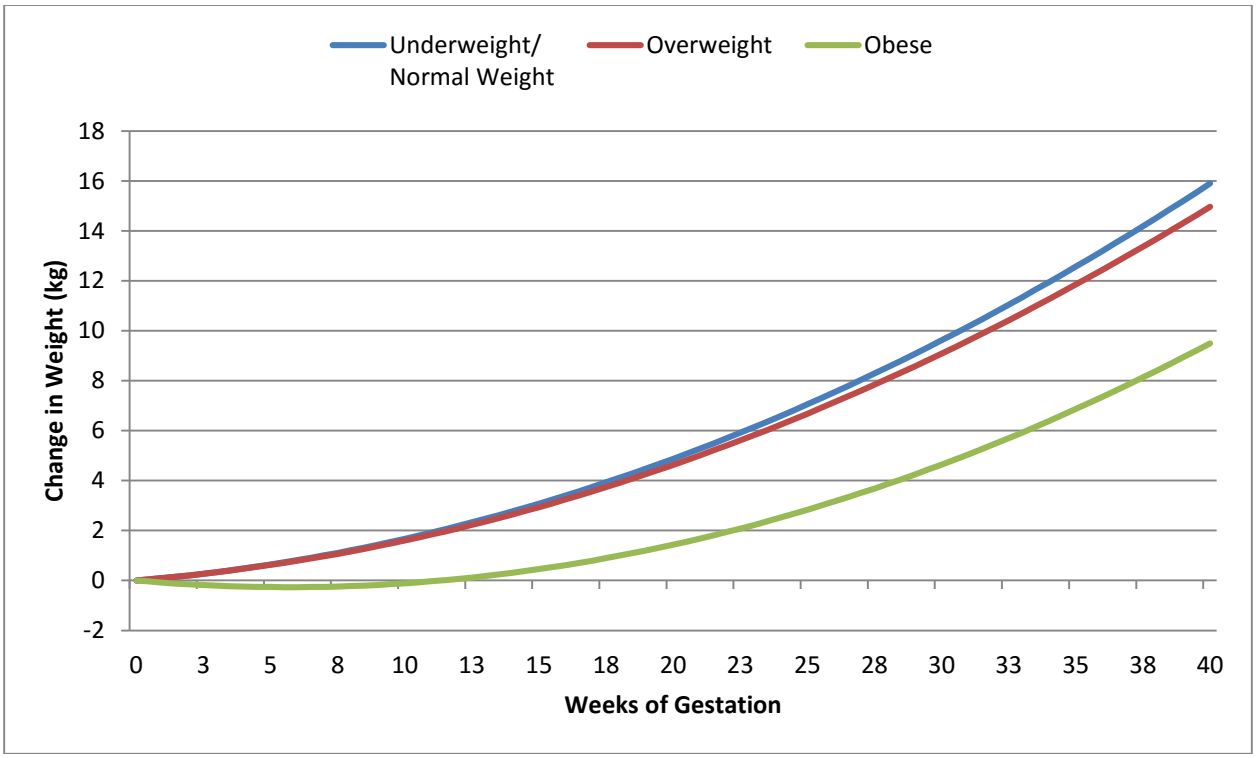


Figure 3. Mean predicted change in weight during pregnancy from mixed effects models with a random effect for individuals[A], stratified by pre-pregnancy BMI[B] for women with SLE in the Hopkins Lupus Pregnancy Cohort (n=211).

[A]Mean weight change = 4.3358 + 0.3928(gestational age) + 0.0077 (gestational age^2) - 0.5002 (overweight) - 3.1870 (obese) - 0.0223(gestational age x overweight) - 0.1603(gestational age x obese) - 0.0005 (gestational age^2 x overweight) + 0.0005 (gestational age^2 x obese)
[B]underweight and normal weight women were combined due to small sample size

CHAPTER 5: PRE-CONCEPTIONAL CARDIOVASCULAR HEALTH AND PREGNANCY OUTCOMES IN WOMEN WITH SYSTEMIC LUPUS ERYTHEMATOSUS

Introduction

Systemic lupus erythematosus (SLE) is an autoimmune disease which largely affects women, with disease onset typically occurring between ages 15 and 44 (1). Although pregnancy outcomes in women with SLE have improved in recent years, most likely due to a paradigm shift in the treatment of SLE during pregnancy, the prevalence of preterm birth (delivery prior to 37 completed weeks' gestation) and infants born small for gestational age (SGA; less than the 10th percentile of weight for gestational age) remains two- to six-times greater in women with SLE, as compared to the general population (65, 146, 147). Well established risk factors for adverse pregnancy outcomes in the general population have not been investigated among women with SLE.

The American Heart Association (AHA)'s 2020 Impact Goals included the development of the concept of "ideal cardiovascular health," which focuses on primary prevention and is composed of seven modifiable cardiovascular metrics: health factors (glucose, cholesterol, and blood pressure) and health behaviors (body mass index, physical activity, diet, and cigarette smoking) (95). Meeting these metrics for ideal cardiovascular health is associated with a lower risk of cardiovascular disease and lower cardiovascular and all-cause mortality rates.

Longitudinal cohort studies report that hypertension, dyslipidemia, and obesity are common co-morbidities in SLE, affecting 30-60% of patients (99-101). Maternal cardiovascular health at conception and during early pregnancy has implications for the *in utero* environment. Obesity at time of conception can lead to alterations in metabolic adjustments during gestation, affecting placental, embryonic, and fetal growth. Increased body fat is associated with increased levels of proinflammatory proteins, and obese women are more likely to enter pregnancy in a state of subclinical inflammation than non-obese women (102-104). In the general population, maternal obesity increases the risk of preeclampsia (148, 149), gestational diabetes (150, 151), and delivering a macrosomic (>4000 g) or large for gestational age infant (105-107).

Studies have shown that hypertension is a risk factor for preterm birth in the general population (108, 109), even when pregnancies affected by preeclampsia were removed from the study population (110). Additionally, chronic hypertension is associated with fetal growth restriction and low birth weight (108, 111, 112), with the risk of preterm SGA births and term SGA births being 5.5 and 1.5-1.7 times greater, respectively, than in woman without hypertension (109).

Previous research, although limited, has demonstrated that increased total cholesterol during the first trimester is associated with preterm birth in the general population, and the association may be modified by maternal inflammation (110, 112, 113). One study reported the risk of very preterm birth (<34 weeks) to be 2.8 times greater among women with high cholesterol compared to women with normal cholesterol (112), and another study estimated a 24% increase in the risk of preterm birth for each 40 mg/dL increase in cholesterol (110).

It has been theorized that maternal risk factors for cardiovascular disease may also be risk factors for fetal growth restriction (114). As SLE is a chronic inflammatory disease, it is important to understand the way these cardiovascular health factors affect preterm birth and fetal growth during SLE pregnancies. We sought to determine the proportion of pregnant women with SLE that meet the AHA's guidelines for ideal cardiovascular health, and to estimate associations of poor and intermediate cardiovascular health with adverse pregnancy outcomes.

Methods

Study population

The Hopkins Lupus Pregnancy Cohort is a subset of the Hopkins Lupus Cohort, which has prospectively followed patients with SLE since 1987, with data available through February 6, 2015. Patients meeting the American College of Rheumatology (ACR) or Systemic Lupus International Collaborating Clinics (SLICC) criteria for SLE (12, 13, 133) were eligible for enrollment in the cohort following informed consent. Patients enrolled in the Hopkins Lupus Cohort and SLE patients seen in the Hopkins Obstetrics Clinics were automatically referred to the Hopkins Lupus Pregnancy Cohort. Outside of Johns Hopkins Hospital, local patients were referred by their local rheumatologists, the Maryland Lupus Foundation and self-referral (126). Pregnant women were seen every 4-6 weeks during pregnancy at the Lupus Center in Baltimore, Maryland by a single rheumatologist. During each visit, a patient's weight,

blood pressure, lupus disease activity [physician global assessment of disease activity (PGA) and SELENA SLEDAI (115, 116)] were measured, medications were updated, and laboratory tests were conducted. Laboratory tests included complete blood count, complement levels (C3 and C4), autoantibodies, total cholesterol, and urinalysis. Pregnancy outcome data were collected from patients at the first postpartum visit to the Lupus Center or by telephone or email, if a woman did not continue her medical care at the Lupus Center.

Pre-conceptional cardiovascular health

Pre-conceptional cardiovascular health was defined according to three of the AHA's metrics, body mass index (BMI), total cholesterol, and blood pressure, using the following criteria: ***BMI***: (1) poor health (obese): ≥30 kg/m^2; (2) intermediate health (overweight): 25-29.9 kg/m^2; (3) ideal health (underweight/normal weight): <25 kg/m^2; ***total cholesterol***: (1) poor health: ≥240 mg/dL; (2) intermediate health: 200–239 mg/dL or treated to goal; (3) ideal health: <200 mg/dL without treatment; ***blood pressure***: (1) poor health: systolic ≥140 or diastolic ≥90 mm Hg; (2) intermediate health: systolic 120–139 or diastolic 80–89 mm Hg or treated to goal; (3) ideal health: <120/<80 mm Hg without treatment. Each metric was coded as a categorical variable, with "ideal health" as the referent group. Due to small sample size, poor health and intermediate health were collapsed into one exposure category for total cholesterol and blood pressure, with ideal health remaining the referent group. Each metric was also analyzed as a continuous variable.

BMI, total cholesterol, and blood pressure at the most recent clinic visit in the one-year prior to conception were used to classify patients' cardiovascular health. If a clinic visit prior to conception was unavailable, the first measurement taken during the first trimester served as a surrogate for preconception health, as it has been demonstrated that these cardiovascular health factors have minimal changes during the first trimester (152, 153).

Pregnancy outcomes

Pregnancy outcomes of interest included gestational age at birth and birth weight for gestational age z-score. Gestational age at birth was based on maternally reported last menstrual period date and date of delivery and categorized as preterm (<37 weeks) and term (≥37 weeks), as well as analyzed as a continuous variable. Birth weight for gestational age z-score was based on US population reference

percentiles of birth weight for singleton infants, stratified by infant sex (134). Z-scores in Oken et al. 2003 were calculated based on the distribution of birth weights for all live births born 22 to 44 weeks gestation in the US, 1999-2000, with a potential range of -2.58 to 2.58. Birth weight for gestational age z-score was analyzed as a continuous variable, as well as categorized based on the percentile of birth weight for gestational age: <10th percentile (small for gestational age; SGA) and >90th percentile (large for gestational age; LGA).

Covariates

Characteristics of interest included race (black vs. non-black), education, age at conception, and duration of SLE. Infant birth date (prior to January 1999 and January 1999-February 2015) was considered a variable of interest due to changes in SLE prescribing patterns. Medication use (anti-malarial, immunosuppressants, prednisone, and prednisone ≥7.5 mg/day) was defined as use ever during pregnancy. Clinical characteristics during pregnancy were defined as ever occurring during pregnancy: renal involvement (renal Lupus Activity Index >1), elevated serum creatinine (>1 mg/dl), high PGA (PGA ≥2), low C3, low C4, and anti-dsDNA (ever positive). Organ system damage at conception was measured by the Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index (SDI), with a score of ≥1 representing the presence of any irreversible organ system damage.

Subject selection

During the study period, there were 515 pregnancies in the Hopkins Lupus Cohort, of which 421 were singleton live births (Figure 4). Pregnancies without any cardiovascular metrics available in the one year prior to conception or first trimester were excluded. Of the 421 births, 309 (73%) had at least one cardiovascular measure (n=291 BMI, n=275 total cholesterol, n=309 blood pressure). Of these 309 births included in our analysis, 63% had a cardiovascular health measurement in the one-year prior to conception; the remaining had the measure during the first trimester. More than one singleton live birth per patient was allowed in the analysis, and these 309 births were from 261 patients,

A greater proportion of live births excluded from the analysis due to missing cardiovascular health data were black and had an infant birth date prior to 1999, compared to the final analysis population. Additionally, excluded births were to patients who had shorter disease duration, lower frequency of anti-malarial use during pregnancy and lower frequency of low C3/C4 (data not shown). Compared to patients

with cardiovascular measures in the year prior to conception, those with measures from the first trimester had shorter disease duration, greater highest PGA during pregnancy, higher frequency of prednisone use during pregnancy, and less often took anti-malarial or immunosuppressants in pregnancy. No differences were seen in live birth outcomes or AHA classification of pre-conceptional cardiovascular health, although patients with pre-pregnancy data had a higher mean total cholesterol and higher mean diastolic blood pressure compared to patients with measures in the first trimester (Appendix 5).

Analysis

Differences in the prevalence of preterm birth, SGA, and LGA among live births by pre-conceptional cardiovascular health were analyzed descriptively by Fischer's exact test. Unadjusted differences in mean gestational age and mean birth weight for gestational age z-score by pre-conceptional cardiovascular health were analyzed by ANOVA. Multivariable logistic regression models estimated odds ratios (OR) and 95% confidence intervals for the association of each maternal cardiovascular health factor and categorical pregnancy outcomes of interest (preterm birth, SGA, and LGA). Multivariable linear regression models estimated associations of each maternal cardiovascular health factor with continuous outcome measures (gestational age at birth and birth weight for gestational age z-score). To account for the correlation between outcomes that would occur from patients contributing more than one pregnancy to this analysis, generalized estimating equations (GEE) with an exchangeable correlation structure were used (136). Confounders were assessed based on combined directed acyclic graph (DAG) minimally sufficient set that was reduced based on a 10% change in beta (β) estimates for parsimony. Models with BMI as the exposure were adjusted for prednisone use during pregnancy and patient race, and blood pressure models were adjusted for renal involvement during pregnancy and patient race. For the exposure of total cholesterol, three adjusted models were estimated: 1) adjusted for patient race and prednisone use during pregnancy; 2) adjusted for patient race and anti-malarial use during pregnancy; and 3) adjusted for patient race, prednisone use during pregnancy, and anti-malarial use during pregnancy. All analyses were conducted with SAS 9.3 (Cary, North Carolina).

Results

The majority of pregnancies were to patients who were white, with a median age at conception of 30 years (Table 9). Anti-malarial, prednisone, and immunosuppressant use during pregnancy were reported in 60%, 51%, and 15% of pregnancies, respectively. The median highest PGA during pregnancy was 1.0, and maternal renal involvement was reported in 26% of pregnancies. There were 95 preterm births (31%), and of the 293 pregnancies with birth weights, 18% were SGA and 4% were LGA (Table 10).

Ideal BMI, total cholesterol, and blood pressure were observed in 56%, 86%, and 51% of pregnancies, respectively (Figure 5). Patients with ideal levels of these 3 cardiovascular risk factors more often had other parameters associated with improved pregnancy outcomes. Patients who were underweight or normal weight (ideal) had higher education, a lower prevalence of renal involvement, lower blood pressure, and were more frequently non-black compared to overweight and obese patients. Patients with ideal total cholesterol had higher education, higher frequency of anti-malarial use, and lower BMI, compared to patients with intermediate/poor total cholesterol. Patients with ideal blood pressure had higher education, lower frequency of prednisone use, lower PGA, lower BMI, and were more frequently non-black, compared to patients with intermediate/poor blood pressure.

In descriptive models, there was a lower frequency of preterm birth among patients who were obese (20%) compared to patients who were overweight and underweight/normal weight (39% and 31%, respectively). Frequency of SGA was lowest in patients who were overweight (8%) compared to obese and underweight/normal weight (22% and 21%, respectively). The frequency of preterm birth was highest in patients with poor total cholesterol (75%) compared to patients with intermediate and ideal total cholesterol (38% and 27%, respectively). The mean gestational age at birth was lower in patients with poor blood pressure (35.8 weeks) compared to patients with intermediate and ideal blood pressure (36.4 weeks and 37.4 weeks, respectively; Table 11). When only patients with a pre-pregnancy cardiovascular measurement were analyzed (n=195), the associations between cardiovascular health and pregnancy outcomes persisted (Appendix 5).

In logistic regression models (Table 12), when adjusted for race and prednisone use, overweight was associated with increased odds of preterm birth compared to underweight/normal weight (OR: 1.38; 95% CI: 0.70, 2.71), while obese was associated with decreased odds of preterm birth compared to underweight/normal weight (OR: 0.50; 95% CI: 0.21, 1.18). Additionally, overweight was associated with decreased odds of SGA compared to underweight/normal weight (OR: 0.26; 95% CI: 0.11, 0.63), adjusted for race and prednisone use. In linear regression models (Table 14), after adjusting for race and prednisone use, gestational age at birth increased with each 1 kg/m^2 increase in BMI (β: 0.06; 95% CI: 0.001, 0.11), and overweight was associated with a higher birth weight-for-gestational age z-score (β: 0.32; 95% CI: 0.06, 0.59).

In logistic regression models adjusted for race and anti-malarial use (Table 12), intermediate/poor total cholesterol was associated with increased odds of preterm birth (OR: 1.91; 95% CI: 0.96, 3.79). No association was seen between cholesterol and SGA. In linear regression models (Table 14), no associations were observed between cholesterol and gestational age at birth or birth-weight-for-gestational age z-score.

The odds of preterm birth was only slightly increased for patients with intermediate/poor blood pressure in logistic regression models (Table 12) after adjustment for race and renal involvement (OR: 1.10; 95% CI: 0.67, 1.79), and no association was observed between blood pressure and SGA. In linear regression models (Table 13), intermediate/poor blood pressure was associated with decreased gestational age at birth (β: -0.96; 95% CI: -1.62, -0.29), adjusted for race and renal involvement.

Discussion

The results of this analysis indicate that pre-conceptional cardiovascular health may have implications for preterm birth in women with SLE. In univariate analyses, women who had ideal levels of weight, cholesterol, or blood pressure had fewer preterm deliveries. Infant size did not appear to be associated with maternal cholesterol or blood pressure, but overweight women had the fewest small for gestational age infants. In multivariable logistic regression models, overweight women had an almost 40% increased risk of preterm birth compared to underweight/normal weight women; however, somewhat surprisingly, overweight women had a 74% decreased risk of a SGA infant compared to

underweight/normal weight women. In linear models, overweight women had a greater birthweight for gestational age z-score compared to underweight/normal weight women in linear models. Of particular interest, there was no observed difference in the frequency of LGA births by pre-conceptional BMI, which is in contrast to pregnancies in the general population (106, 154, 155). However, as power is limited by the low frequency of LGA births in the analysis, these results should be considered preliminary.

In the general population, an analysis of women of reproductive age (20-44 years) from the National Health and Nutrition Examination Survey (NHANES) estimated the prevalence of overweight and obesity in the United States in 2003-2008 to be 23% and 29%, respectively (156). Our cohort had a similar distribution of pre-pregnancy BMI, with 24% and 20% of women overweight and obese, respectively. Analyses of the Nationwide Inpatient Sample reported that the diagnosis of hypertension prior to pregnancy is more common among women with SLE than women without SLE (147). Additionally, among women who gave birth in the United States in 2002, women with SLE had almost three times the prevalence of hypertensive disorders than women of the general population, with 8% of the general population having a hypertensive disorder (157). As expected, the prevalence of poor and intermediate pre-pregnancy blood pressure was high in this cohort, with approximately half of patients having blood pressure ≥120/≥80 mm Hg or blood pressure treated to goal.

The effects of pre-conceptional cardiovascular health on pregnancy outcomes seen in this analysis were consistent with studies of the general population. In the general population, there is an association of pre-pregnancy BMI and preterm birth, with the frequency of preterm birth being highest among underweight women and obese women (105, 158). It is important to note, however, that the indication of preterm birth should be considered in its association of pre-pregnancy BMI. Reasons for a medically indicated preterm delivery in SLE include maternal blood pressure, preeclampsia, proteinuria, decreased amniotic fluid volume, intrauterine growth restriction, and HELLP syndrome (hemolysis, elevated liver enzymes and low platelets) (6). Several studies have demonstrated an increased risk of indicated preterm birth but decreased risk of spontaneous preterm birth in obese patients in the general population (159-161). One study estimated a 43% decrease in the risk of spontaneous preterm birth compared to women with normal BMI; however, a higher frequency of preterm births in obese women were indicated compared to women with normal BMI (161). Although data are limited, one study reported

that 75% of preterm births in women with SLE were medically indicated (50). A limitation of the present analysis is data specifying indication of preterm births were not collected; therefore, we were unable to determine if pre-conception cardiovascular health increased the risk of spontaneous preterm birth, indicated preterm birth, or both.

Our findings of increased risk of preterm birth in patients with intermediate and poor pre-conception cholesterol are supported by previous general population studies. An analysis of the Coronary Artery Risk Development in Young Adults Study (CARDIA) study reported a U-shaped association of pre-pregnancy cholesterol and preterm birth, with the lowest and highest tertiles of pre-pregnancy cholesterol increasing the risk of preterm birth (162). This association was supported by a case-control analysis in the Pregnancy Exposures and Preeclampsia Prevention (PEPP) study, which found the risk of preterm birth in patients with high cholesterol during the first 15 weeks of pregnancy to be almost three times the risk of patients with normal cholesterol (112). The results of our linear regression models show a decrease in gestational age at birth in patients with intermediate and poor pre-conception blood pressure. This supports previous findings in both the general population and SLE cohorts that hypertension is associated with gestational age at birth (108-110, 163).

Our study suffered from some limitations. Cardiovascular health data were not available for all live births in the cohort, and it is unknown how the cardiovascular health of these patients differed. Data were also unavailable in the cohort for the four remaining AHA cardiovascular metrics (glucose, physical activity, diet, and cigarette smoking); therefore, we were unable to assess the combined effects of cardiovascular risk factors. Additionally, the data were collected at a single academic center. While this is favorable with respects to consistency in the treatment of patients and data collection, the cohort described in this analysis may not be representative of all SLE patients. Finally, the sample size of the analytic cohort limited our statistical power, particularly for discrete outcomes (preterm birth, SGA, and LGA). While the cohort is larger than other SLE pregnancy cohorts, the modest sample size does not provide sufficient power to detect small differences in outcomes. Even so, the results of analyses with continuous variable mirrored that of categorical variables, giving us confidence in our results.

Conclusions

The findings of our analysis have important implications for SLE patients during pregnancy. Of particular interest is the apparent inverse association of preterm birth in obese patients, but an increased risk of preterm birth in overweight patients. This suggests that efforts to normalize maternal weight prior to pregnancy may improve pregnancy outcomes. Additionally, having a further understanding of SLE patients who are able to maintain ideal cardiovascular health will be important in order to develop future targeted treatments. Previous studies have found that among patients with SLE, pregnancy increases the risk of future major cardiovascular events and a poor pregnancy outcome increases the risk cardiovascular mortality (164). Interventions to improve the cardiovascular health of patients prior to pregnancy would improve pregnancy outcomes, as well as benefit the long-term health of SLE patients.

This analysis is the first to examine the AHA's guidelines for cardiovascular health in patients with SLE prior to conception, as well as determine the effects of suboptimal pre-conceptional cardiovascular health on live birth outcomes. The analysis highlights the importance of SLE patients having BMI, total cholesterol, and blood pressure within the ideal range prior to pregnancy in order to reduce the risk of preterm births and improve the overall cardiovascular health of SLE patients.

Table 9. Population characteristics in the Hopkins Lupus Pregnancy Cohort (n=309)

	N=309 pregnancies	N = 261 patients
	n (%)	n (%)
Race		
White	184 (60%)	151 (58%)
Black	93 (30%)	80 (31%)
Other	32 (10%)	30 (11%)
Education		
HS Education (≤12 years)	101 (33%)	81 (31%)
College (13-16 years)	141 (46%)	120 (46%)
Greater than College (>16 years)	67 (22%)	60 (23%)
Infant birth date		
Prior to January 1999	117 (38%)	
January 1999 – February 2015	192 (62%)	
Medication use during pregnancy[1]		
Anti-malarial	184 (60%)	
Immunosuppressant	48 (15%)	
Prednisone	160 (51%)	
Prednisone ≥7.5 mg/day among prednisone users	116 (73%)	
Clinical characteristics[A]		
Renal involvement during pregnancy (LAI>1)	79 (26%)	
Elevated serum creatinine during pregnancy (>1)	24 (8%)	
High PGA during pregnancy (PGA ≥2)	49 (16%)	
SDI ≥1 at conception	114 (37%)	
Low C3 during pregnancy	74 (24%)	
Low C4 during pregnancy	106 (34%)	
Anti-dsDNA+ during pregnancy	115 (37%)	
	Median (IQR)	
Age at conception, years	29.9 (26.7-33.2)	
Disease duration, years	5.5 (2.1-9.3)	
Highest PGA during pregnancy (scale: 0-3)	1.0 (0.5-1.5)	
SDI at conception	0 (0-3)	
Highest daily prednisone dose during pregnancy, mg	2.5 (0-15.0)	
BMI, kg/m^2	24.3 (21.3-29.2)	
Total cholesterol, mg/dL	162.0 (142.0-184.0)	
Systolic blood pressure, mm Hg	116.0 (106.0-126.0)	
Diastolic blood pressure, mm Hg	70.0 (64.0-80.0)	

[A]categories not mutually exclusive; women can be in multiple categories, therefore, percentages add up to more than 100%

Abbreviations: BMI, body mass index; C3, complement 3; C4, complement 4; HS, high school; LAI, Lupus Activity Index; PGA: Physician Global Assessment of Disease Activity; SDI: SLICC/ACR Damage Index

Table 10. Live birth outcomes in the Hopkins Lupus Pregnancy Cohort (n=309)

	n (%)
Small for gestational age (n=293)	53 (18%)
Large for gestational age (n=293)	12 (4%)
Preterm birth	95 (31%)
Pregnancy induced hypertension (n=252)	15 (6%)
Preeclampsia (n=257)	30 (12%)
Caesarian section (n=256)	100 (39%)
Premature rupture of membranes (n=255)	39 (15%)
	Median (IQR)
Gestational age at birth (weeks)	38.0 (36.0-39.0)
Birth weight percentile (n=293)	31.0 (12.0-53.0)
Birth weight z-score (n=293)	-0.51 (-1.20 – 0.06)
Birth weight (g) (n=293)	2920.0 (2506.1 – 3309.0)

Table 11. Mean gestational age and birth weight z-scores by pre-conceptional cardiovascular health, with ANOVA tests for differences in means in the Hopkins Lupus Pregnancy Cohort (n=309)

	Gestational Age	Birth Weight Z-Score
	Mean Weeks (SD)	Mean (SD)
Body mass index		
Ideal health (under/normal weight; <25 kg/m^2)	36.7 (3.9)	-0.58 (0.92)
Intermediate health (overweight; 25-29.9 kg/m^2)	36.8 (2.6)	-0.28 (0.82)
Poor health (obese; ≥30 kg/m^2)	37.4 (3.1)	-0.51 (1.06)
ANOVA p-value	*0.3*	*0.09*
Total cholesterol		
Ideal health (<200 mg/dL)	37.0 (3.2)	-0.48 (0.94)
Intermediate health (200–239 mg/dL or treated to goal)	36.8 (2.3)	-0.48 (0.95)
Poor health (≥240 mg/dL)	34.9 (3.9)	-0.53 (0.60)
ANOVA p-value	*0.2*	*1.0*
Blood pressure		
Ideal health (<120/<80 mm Hg)	37.4 (2.6)	-0.48 (0.98)
Intermediate health (Systolic 120–139 or Diastolic 80–89 mm Hg or treated to goal)	36.4 (3.3)	-0.50 (0.91)
Poor health (Systolic ≥140 or Diastolic ≥90 mm Hg)	35.8 (4.1)	-0.55 (0.72)
ANOVA p-value	*0.003*	*0.9*

Table 12. Multivariable logistic regression models for association of pre-conceptional cardiovascular health and pregnancy outcomes in SLE in the Hopkins Lupus Pregnancy Cohort.

	Preterm Birth		SGA	
	OR (95% CI)	AOR (95% CI)	OR (95% CI)	AOR (95% CI)
Body Mass Index[A]				
Ideal Health (under/normal weight; n=163)	1.0	1.0	1.0	1.0
Intermediate (overweight; n=69)	1.39 (0.82, 2.36)	1.38 (0.70, 2.71)[D]	0.35 (0.15, 0.82)	0.26 (0.11, 0.63)[D]
Poor Health (obese; n=59)	0.56 (0.28, 1.13)	0.50 (0.21, 1.18)[D]	0.95 (0.44, 2.05)	0.92 (0.42, 2.05)[D]
Total Cholesterol[B]				
Ideal Health (n=235)	1.0	1.0	1.0	1.0
Intermediate/Poor Health (n=40)	2.27 (1.15, 4.46)	2.21 (1.06, 4.62)[D]	0.57 (0.21, 1.54)	0.41 (0.14, 1.26)[D]
		1.91 (0.96, 3.79)[E]		0.58 (0.21, 1.61)[E]
		1.93 (0.92, 4.04)[F]		0.44 (0.14, 1.38)[F]
Blood Pressure[C]				
Ideal Health (n=158)	1.0	1.0	1.0	1.0
Intermediate/Poor Health (=151)	1.32 (0.82, 2.12)	1.10 (0.67, 1.79)[G]	0.68 (0.39, 1.20)	0.60 (0.33, 1.10)[G]
Continuous variables				
BMI, kg/m^2 (n=291)	0.97 (0.93, 1.01)	0.95 (0.91, 1.00)[D]	0.99 (0.94, 1.04)	0.98 (0.93, 1.04)[D]
Total cholesterol, 10 mg/dL (n=275)	1.11 (1.03, 1.19)	1.10 (1.01, 1.19)[D]	0.91 (0.82, 1.02)	0.90 (0.80, 1.01)[D]
		1.08 (1.01, 1.16)[E]		0.92 (0.82, 1.02)[E]
		1.09 (1.00, 1.18)[F]		0.90 (0.80, 1.01)[F]
Systolic blood pressure, 10 mmHg (n=309)	1.15 (0.99, 1.34)	1.08 (0.92, 1.28)[G]	0.88 (0.73, 1.06)	0.85 (0.70, 1.04)[G]
Diastolic blood pressure, 10 mmHg (n=309)	1.25 (0.99, 1.58)	1.18 (0.93, 1.50)[G]	0.79 (0.59, 1.06)	0.75 (0.56, 1.02)[G]

[A] Body mass index: (1) poor health: ≥30 kg/m^2; (2) intermediate health: 25-29.9 kg/m^2; (3) ideal health: <25 kg/m^2

[B] Total cholesterol: (1) poor health: ≥240 mg/dL; (2) intermediate health: 200–239 mg/dL or treated to goal; (3) ideal health: <200 mg/Dl

[C] Blood pressure: (1) poor health: Systolic ≥140 or Diastolic ≥90 mm Hg; (2) intermediate health: Systolic 120–139 or Diastolic 80–89 mm Hg or treated to goal; (3) ideal health: <120/<80 mm Hg

[D] Adjusted for race (black vs. non-black) and prednisone use ever during pregnancy

[E] Adjusted for race (black vs. non-black) and anti-malarial use ever during pregnancy

[F] Adjusted for race (black vs. non-black), prednisone use ever during pregnancy, and anti-malarial use ever during pregnancy

[G] Adjusted for race (black vs. non-black) and renal involvement during pregnancy (Renal LAI ≥1)

Table 13. Multivariable linear regression models for association of pre-conceptional cardiovascular health and pregnancy outcomes in SLE in the Hopkins Lupus Pregnancy Cohort.

	Gestational Age		Birthweight for Gestational Age Z-Score	
	β (95% CI)	Adjusted β (95% CI)	β (95% CI)	Adjusted β (95% CI)
Body Mass Index[A]				
Ideal Health (under/normal weight; n=163)	Ref	Ref	Ref	Ref
Intermediate (overweight; n=69)	0.19 (-0.65, 1.01)	0.14 (-0.63, 0.93)[D]	0.29 (0.03, 0.56)	0.32 (0.06, 0.59)[D]
Poor Health (obese; n=59)	0.75 (-0.21, 1.71)	0.70 (-0.24, 1.65)[D]	0.08 (-0.24, 0.41)	0.14 (-0.18, 0.45)[D]
Total Cholesterol[B]				
Ideal Health (n=235)	Ref	Ref	Ref	Ref
Intermediate/Poor Health (n=40)	-0.53 (-1.46, 0.40)	-0.43 (-1.28, 0.41)[D]	0.02 (-0.29, 0.33)	0.03 (-0.28, 0.34)[D]
		-0.39 (-1.30, 0.51)[E]		-0.02 (-0.32, 0.29)[E]
		-0.37 (-1.22, 0.48)[F]		-0.02 (-0.33, 0.30)[F]
Blood Pressure[C]				
Ideal Health (n=158)	Ref	Ref	Ref	Ref
Intermediate/Poor Health (=151)	-1.14 (-1.83, -0.45)	-0.96 (-1.62, -0.29)[G]	0.02 (-0.19, 0.24)	0.09 (-0.12, 0.31)[G]
Continuous variables				
BMI, kg/m^2 (n=291)	0.05 (-0.004, 0.11)	0.06 (0.001, 0.11)[D]	0.01 (-0.01, 0.03)	0.02 (-0.01, 0.04)[D]
Total cholesterol, 10 mg/dL (n=275)	-0.07 (-0.18, 0.04)	-0.06 (-0.15, 0.04)[D]	0.01 (-0.02, 0.03)	0.01 (-0.02, 0.04)[D]
		-0.06 (-0.16, 0.04)[E]		0.004 (-0.02, 0.03)[E]
		-0.05 (-0.14, 0.04)[F]		0.005 (-0.02, 0.03)[F]
Systolic blood pressure, 10 mmHg (n=309)	-0.46 (-0.71, -0.21)	-0.39 (-0.63, -0.15)[G]	0.004 (-0.06, 0.07)	0.03 (-0.04, 0.10)[G]
Diastolic blood pressure, 10 mmHg (n=309)	-0.60 (-0.98, -0.22)	-0.52 (-0.89, -0.14)[G]	0.01 (-0.09, 0.11)	0.04 (-0.06, 0.15)[G]

[A] Body mass index: (1) poor health: ≥30 kg/m^2; (2) intermediate health: 25-29.9 kg/m^2; (3) ideal health: <25 kg/m^2

[B] Total cholesterol: (1) poor health: ≥240 mg/dL; (2) intermediate health: 200–239 mg/dL or treated to goal; (3) ideal health: <200 mg/Dl

[C] Blood pressure: (1) poor health: Systolic ≥140 or Diastolic ≥90 mm Hg; (2) intermediate health: Systolic 120–139 or Diastolic 80–89 mm Hg or treated to goal; (3) ideal health: <120/<80 mm Hg

[D] Adjusted for race (black vs. non-black) and prednisone use ever during pregnancy

[E] Adjusted for race (black vs. non-black) and anti-malarial use ever during pregnancy

[F] Adjusted for race (black vs. non-black), prednisone use ever during pregnancy, and anti-malarial use ever during pregnancy

[G] Adjusted for race (black vs. non-black) and renal involvement during pregnancy (Renal LAI ≥1)

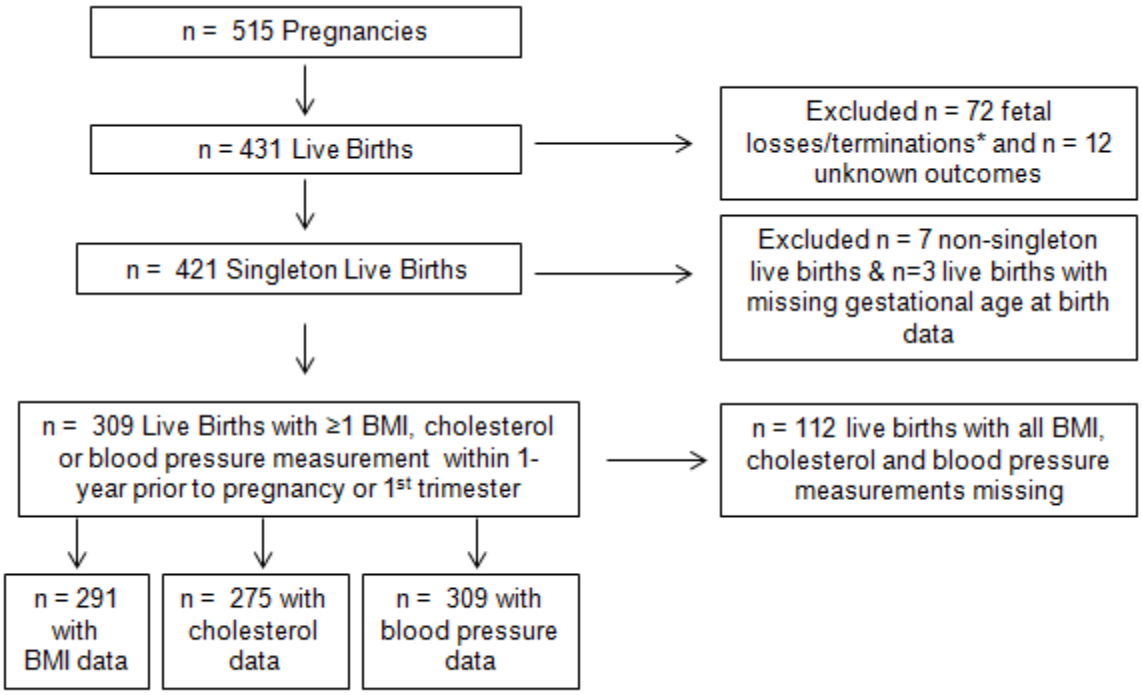


Figure 4. Aim 2 Study population for the Hopkins Lupus Pregnancy Cohort, 1987 to February 2015.

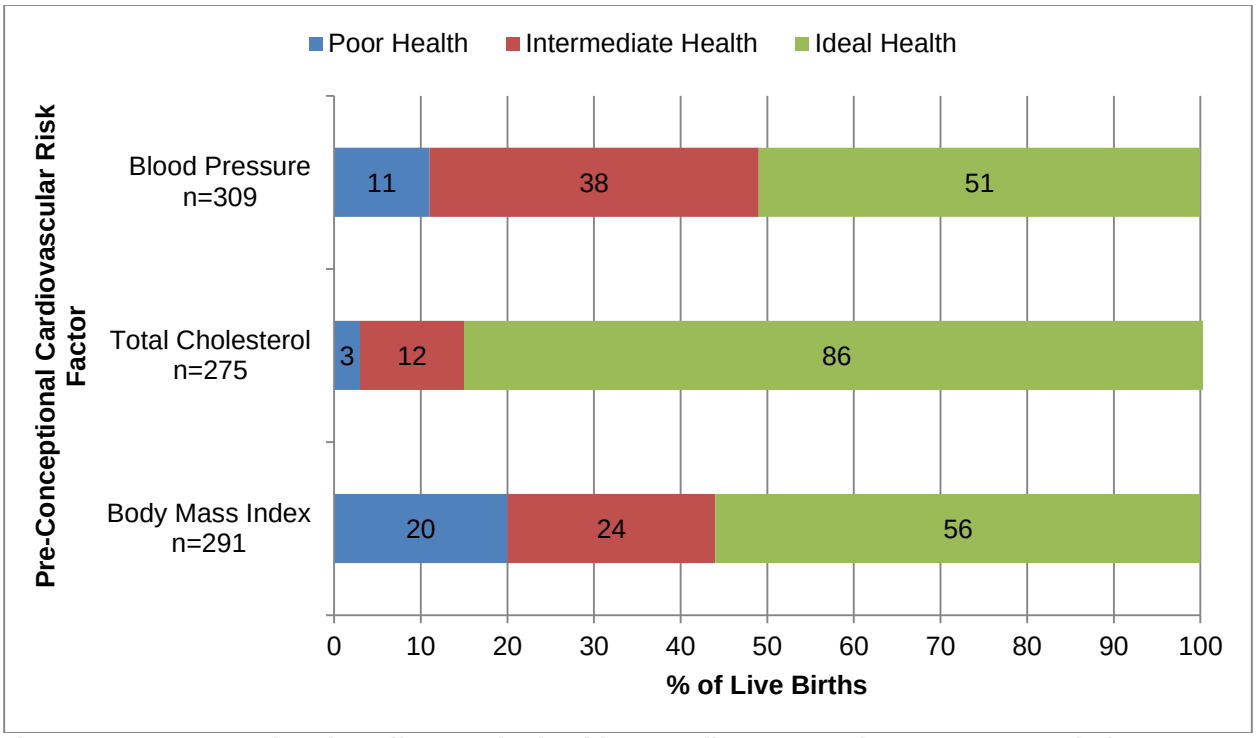


Figure 5. Pre-conceptional cardiovascular health according to American Heart Association criteria* in the Hopkins Lupus Pregnancy Cohort.

*Body mass index: (1) poor health (obese): ≥30 kg/m^2; (2) intermediate health (overweight): 25-29.9 kg/m^2; (3) ideal health (under/normal weight): <25 kg/m^2
Total cholesterol: (1) poor health: ≥240 mg/dL; (2) intermediate health: 200–239 mg/dL or treated to goal; (3) ideal health: <200 mg/dL
Blood pressure: (1) poor health: Systolic ≥140 or Diastolic ≥90 mm Hg; (2) intermediate health: Systolic 120–139 or Diastolic 80–89 mm Hg or treated to goal; (3) ideal health: <120/<80 mm Hg

CHAPTER 6: EFFECT OF PREGNANCY ON DISEASE FLARES IN PATIENTS WITH SYSTEMIC LUPUS ERYTHEMATOSUS

Introduction

Systemic lupus erythematosus (SLE) is characterized by fluctuations of disease activity, with periods of high disease activity (i.e., flares) followed by periods of low disease activity. Disease indices have been designed and validated to describe the degree of a patient's disease activity, including the SELENA revision of the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) (115-118), British Isles Lupus Assessment Group (BILAG) index (119, 120), Systemic Lupus Activity Measure (SLAM) Index (121, 122) and European Consensus Lupus Activity Measurement (ECLAM) index (123-125). The effect of pregnancy on disease activity and flares in SLE has long been debated. Previous research has found that between 19 and 68% of women with SLE experience a flare during pregnancy (7, 39, 50-53, 57, 126-129). Risk factors for flare during pregnancy include active disease at conception, prednisone use, kidney disease and previous flares (52, 53, 57).

There are conflicting results about the effect pregnancy has on the health of SLE women. Some studies report an increased rate of flares during pregnancy, while others report no difference in disease activity during pregnancy or postpartum. The rate of flares per person-month in pregnancy ranges from 0.06 – 0.14, compared to 0.04 – 0.05 in non-pregnant SLE patients (126, 127, 130, 131). A study by Lockshin et al. (132) analyzed flare characteristics of pregnant and non-pregnant SLE patients, including laboratory values (urine protein, anti-dsDNA, complement, hemoglobin, etc.) and symptoms (rash, fever, serositis, arthritis, neurologic events, etc.), and did not find a difference between women who were pregnant and women who were not. In contrast, Petri et al. (126) found that the rate of flare was greater during pregnancy than in non-pregnant controls, and a subsequent analysis by Ruiz-Irastorza et al. (127) found that the rates of flare during pregnancy and a 6-week postpartum period were increased compared to non-pregnant, age-matched controls.

A limitation of the current literature is the inconsistency in which flares are defined. Different scales or sets of parameters are used in each study, making it difficult to make comparisons across studies. Many previous studies were also limited by a small sample size, which reduced power to determine differences in the rate of flares between pregnant and non-pregnant SLE patients. Additionally, previous studies did not included patients followed by protocol at set intervals during pregnancy. Understanding the effect pregnancy has on disease activity is clinically significant for the patient, as previous research has found that high disease activity during pregnancy is associated with preterm births and pregnancy loss (6, 7, 54). Additionally, examining the rate of flares during the postpartum period compared to unexposed periods will be important in determining if patients need to be more closely monitored in the year following pregnancy. The objective of the current analysis was to estimate the effect of pregnancy on disease activity (i.e., disease flares) in SLE using two variations of Cox proportional hazards models, the counting process Cox and the standard Cox. Models included two exposures, pregnancy and a 1-year postpartum period, and the rates of flares during each of these periods were compared to the rate of flares when women were neither pregnant nor in a postpartum period (>12 months after delivery).

Methods

Study population

The Hopkins Lupus Pregnancy Cohort is a subset of the Hopkins Lupus Cohort, which has prospectively followed patients with SLE since 1987, with data available through February 6, 2015. Patients meeting the American College of Rheumatology (ACR) or Systemic Lupus International Collaborating Clinics (SLICC) criteria for SLE (12, 13, 133) were eligible for enrollment in the cohort following informed consent. Patients enrolled in the Hopkins Lupus Cohort and SLE patients seen in the Hopkins Obstetrics Clinics were automatically referred to the Hopkins Lupus Pregnancy Cohort. Outside of Johns Hopkins Hospital, local patients were referred by their local rheumatologists, the Maryland Lupus Foundation and self-referral (126). Pregnant women were seen every 4-6 weeks during pregnancy at the Lupus Center in Baltimore, Maryland by a single rheumatologist. During each visit, a patient's weight, blood pressure, lupus disease activity [Physician Global Assessment of disease activity (PGA) and SELENA SLEDAI (115, 116)]

were measured, medications were updated, and laboratory tests were conducted. Laboratory tests included complete blood count, complement levels (C3 and C4), anti-dsDNA, antiphospholipid antibodies, total cholesterol, and urinalysis. Pregnancy outcome data were collected from patients at the first postpartum visit to the Lupus Center or by telephone or email, if a woman did not continue her medical care at the Lupus Center.

Exposures

Exposure was classified as pregnancy (yes/no), 1-year postpartum period (yes/no), or non-pregnant/non-postpartum period (unexposed). The exposure variables were included as time-varying covariates, so as to include all observations for an individual (including, for example, pre-pregnancy observations on women who became pregnant).

Outcomes

Disease flares can be analyzed according to several disease indices, and this analysis used PGA and SELENA SLEDAI. PGA is a disease activity index ranging from 0 to 3, with 0 being no activity and 3 being severe disease activity (135). SELENA SLEDAI is a weighted disease activity index for activity related to SLE present within the previous 10 days, with a score range of 0 to 105 (118). Flares during follow-up were classified according to two different criteria:

3. Change in PGA ≥1 from previous visit
4. Change in SELENA SLEDAI ≥4 from the previous visit.

Subject selection

During the study period, there were 2417 SLE patients observed in the Hopkins Lupus Cohort, of which 2229 were female. Fifteen female patients were removed due to lack of complete information on pregnancies, and an additional 350 patients were removed because SLE diagnosis occurred after age 45 years. Of these patients, 1426 had more than one study visit to calculate flares; however, 77 of patients were observed only during pregnancy and were removed from the study population due to never contributing to unexposed person-time. A sensitivity analysis including these 77 patients can be found in

Appendix 6. The final analytic cohort consisted of 1349 women; 999 of these women had a history of pregnancy or an observed pregnancy during the study period. Of the 515 pregnancies in the Hopkins Lupus Cohort, n=398 pregnancies in 304 patients were included. There were n=381 observed 1-year postpartum periods, with at least one visit during the postpartum period.

Analysis

All women with SLE in the Hopkins Lupus Cohort between the ages of 15 and 45 were included in the analysis, regardless of pregnancy status. Women with only one measurement of disease activity were excluded. The time of entry into the Hopkins Lupus Cohort was considered the initial measurement for all women. Patients were right censored and removed from the risk set at age 45 (end of reproductive years), menopause (if prior to age 45 years), loss to follow-up, death, or February 6, 2015, the end of follow-up. If patients had a gap of more than one year in study visits, patients were considered lost to follow-up, but were allowed to re-enter the cohort when study visits resumed. The time between when a patient exited and re-entered the cohort did not contribute to person-time at risk. This method was utilized due to a disease activity measurement from more than a year previous not being a suitable comparator to calculate disease flare.

Crude incidence rates were calculated as the observed number of flares / total person-time for each exposure period. Incidence rate ratios and corresponding 95% confidence intervals were calculated for pregnancy vs. unexposed periods and postpartum vs. unexposed periods. The analysis used two separate variations of Cox models to estimate the hazard rate ratio of flares in pregnancy and postpartum periods compared to unexposed periods. The first model was the standard counting process Cox proportional hazards model, which accounted for repeated measured and assumed that the order of the events of flares did not need to be taken into consideration. The second model was a stratified Cox model, a conditional model that did not assume independence of multiple events of flare (165). Instead, a stratum for the time interval number was included in the model so a patient was not at risk for a second flare without having experienced a previous flare. Hazard ratios and 95% confidence intervals (95% CI) were estimated for each model.

If a woman had more than one pregnancy, all pregnancies (as well as postpartum periods) were included in the analysis. Due to repeated events of flares being counted in the same patient and patients being allowed to exit and re-enter the analytic cohort, 95% confidence intervals were estimated with 1,000 bootstrap replications sampled with replacement (138). Using the same model, relative hazard rates of flare were calculated between 1) pregnant and unexposed periods and 2) postpartum and unexposed periods. To account for the time-varying exposures, a new patient ID was created for each patient which changed when the exposure changed, and both the original ID and new ID were included in the Cox models. Potential covariates of interest included patient race (black vs. non-black), age at SLE diagnosis, age at baseline, and duration of disease at baseline. Prednisone and hydroxychloroquine were explored as time-varying covariates. Confounders were defined by a 10% change in beta (β) estimates when included in the model. None of the covariates were found to be confounders in any models. Effect measure modifiers were identified by likelihood ratio test (α=0.20). To determine if the association of pregnancy and the postpartum period with flares has changed over time, we conducted a sensitivity analysis limited to person-time since the year 2000 through the end of follow-up (February 6, 2015).

In order to determine if all women in the Hopkins Lupus Cohort were an appropriate comparator group for women who became pregnant, two sensitivity analyses were performed. The first included only women who had a history of pregnancy or had an observed pregnancy while in the Hopkins Lupus Cohort (n=999). The second sensitivity analysis included only women who had an observed pregnancy while in the Hopkins Lupus Cohort (n=304). All analyses were conducted in SAS 9.3 (Cary, North Carolina).

Results

The median age at baseline was 30.6 years of the 1349 patients in the total cohort and 29.4 years at the first pregnancy observed in the cohort (Table 14). The majority of patients were white (49% of the total cohort and 57% of pregnant women), and the median duration of SLE at baseline was 2.0 years. The median follow-up was 3.9 years (IQR: 1.3-10.4 years). Of the 398 pregnancies, 85% were live births, of which 29% were preterm and 24% were small for gestational age (Table 15).

For the total cohort, the incidence of flares based on the PGA definition was 60.7 per 100 person-years (PY) during pregnancy compared to 40.2 per 100 PY (Table 16) during unexposed periods (crude IRR: 1.51; 95% CI: 1.27, 1.80). The incidence of flare during the postpartum period was 39.9 per 100 PY,

and no increased incidence was observed during postpartum periods compared to unexposed periods (crude IRR: 0.99; 95% CI: 0.84, 1.17). Rate ratios were also estimated in counting process Cox models (Table 17), where there was an increased rate of flare during pregnancy (HR: 1.44; 95% CI: 1.14, 1.75) but no evidence of an increased rate during postpartum period (HR: 0.94; 95% CI: 0.76, 1.13), when compared to unexposed periods. In stratified Cox models, the increased rate of flare during pregnancy persisted (HR: 1.59; 95% CI: 1.27, 1.96), and there was no evidence of an increased rate during the postpartum periods compared to unexposed periods.

In sensitivity analyses, the incidence of PGA flares during unexposed periods decreased when only patients with a history of pregnancy or observed pregnancy were in the analysis (39.3 per 100 PY) and when only patients with an observed pregnancy were in the analysis (35.9 per 100 PY). Point estimates for pregnancy compared to unexposed periods, as well as postpartum compared to unexposed periods, increased in both sensitivity analyses compared to the primary analysis in the total cohort. When the 77 patients with no observed unexposed periods were included in the analysis (see Appendix 6), results were similar, with an increased rate of flare observed during pregnancy compared to unexposed times. However, hazards ratios for postpartum compared to unexposed periods showed no evidence of an increased incidence of flare during postpartum periods.

When flares were defined as a ≥4 change in SELENA SLEDAI score, results were comparable to the PGA definition of flare. In the overall cohort, the crude incidence of flare during pregnancy was 63.4 per 100 PY (Table 16), compared to 47.3 per 100 PY during unexposed periods (crude IRR: 1.34; 95% CI: 1.13, 1.59). No increased rate of flares was observed during postpartum periods compared to unexposed periods (IRR: 0.97; 95% CI: 0.83, 1.13). Counting process Cox models estimated similar associations (Table 18), with an increased rate of flare during pregnancy (HR: 1.30; 95% CI: 1.04, 1.62) compared to unexposed periods, but no evidence of an increased rate during postpartum periods (HR: 0.93; 95% CI: 0.75, 1.12). In stratified Cox models, the increased rate of flare during pregnancy remained (HR: 1.57; 95% CI: 1.25, 1.92), and there was no evidence of an increased rate of flare during postpartum periods compared to unexposed periods (HR: 1.09; 95% CI: 0.89, 1.32).

Similar to models of PGA flares, hazard ratios increased in sensitivity analyses, as the crude incidence of SELENA SLEDAI flare decreased during unexposed periods (44.7 per 100 PY when only

women with a history of pregnancy or ≥1 observed pregnancy were included and 39.5 per 100 PY when only women with ≥1 observed pregnancy were included). When the 77 patients with no observed unexposed periods were included in the analysis (see Appendix 6), the increased rate of flare during pregnancy compared to unexposed periods persisted. The hazard ratio of flares in postpartum periods to unexposed periods decreased from the estimates in the primary analysis, although an increased rate of flare was still estimated in stratified Cox models.

In counting process Cox models limited to only women with ≥1 observed pregnancy, race was found to be an effect modifier in the association when flares were measured according to SELENA SLEDAI, but not PGA. For the association of pregnancy compared to unexposed periods, the HR was 1.36 (95% CI: 0.88, 1.96) in black patients and 1.70 (95% CI: 1.18, 2.31) in non-black patients. In the association of postpartum vs. unexposed periods, the HR was 0.91 (95% CI: 0.65, 1.23) in black patients and 1.27 (95% CI: 0.92, 1.68) in non-black patients.

Hydroxychloroquine use was found to be an effect modifier in the association of pregnancy and flares. When flares were measured by PGA, counting process Cox models estimated the HR of flares in pregnancy compared to unexposed periods to be 1.74 (95% CI: 1.27, 2.29) for patients with no hydroxychloroquine use and 1.15 (95% CI: 0.81, 1.54) for patients with hydroxychloroquine use (likelihood ratio p-value: 0.02; Table 19). This modification by hydroxychloroquine use was also observed in stratified Cox models. There was no evidence in any models that hydroxychloroquine use modified the association of flares in the postpartum period compared to unexposed periods. When flares were measured by SELENA SLEDAI, counting process Cox models estimated the HR of flares in pregnancy compared to unexposed periods to be 1.50 (95% CI: 1.11, 1.98) for patients with no hydroxychloroquine use and 1.14 (95% CI: 0.80, 1.52) for patients with hydroxychloroquine use (likelihood ratio p-value=0.12; Table 20). There was no evidence of modification in the overall cohort by hydroxychloroquine use in stratified models.

Prednisone use was only found to be an effect modifier in the association of pregnancy and flares in the sensitivity cohort patients with an observed pregnancy when flares were defined by SELENA SLEDAI (Appendix 6). Counting process Cox models estimated the HR of flares in pregnancy compared to unexposed periods to be 1.84 (95% CI: 1.19, 2.65) in patients with no prednisone use and 1.38 (95%

CI: 0.99, 1.85) in patients with prednisone use (likelihood ratio p-value: 0.14). This association persisted in stratified Cox models. There was no evidence for modification by prednisone use in PGA models or other SELENA SLEDAI models.

When the cohort was limited to only visits after the year 2000, results were similar for flares defined by PGA (Table 21). Counting process Cox models estimated the HR of flares in pregnancy compared to unexposed periods to be 1.31 (95% CI: 0.93, 1.72), and there was no evidence of an increased rate of flare during the postpartum period (HR: 0.95; 95% CI: 0.68, 1.25). In contrast, when flares were defined by SELENA SLEDAI (Table 22), there was no evidence of an increased rate of flare during pregnancy (HR: 1.09; 95% CI: 0.72, 1.26).

In the sensitivity analysis limited to time since the year 2000, we found the modification of HCQ use remained when flares were measured by PGA (Table 23), with counting process Cox models estimating a HR of 1.68 (95% CI: 0.95, 2.64) among patients without HCQ use in pregnancy compared to unexposed periods and a HR of 1.16 (95% CI: 0.77, 1.61) among patients with HCQ use (likelihood ratio p-value=0.18). In contrast, when flares were measured by SELENA-SLEDAI (Table 24), there was no evidence of an association in counting process Cox models for pregnancy compared to unexposed or postpartum compared to unexposed among patients who were exposed and among patients who unexposed to HCQ. Of interest, there appeared to be a decreased association among patients who were not exposed to HCQ. The number of flares and total person-time for each time period stratified by HCQ use can be found in Appendix 6.4 for PGA flares and Appendix 6.5 for SELENA-SLEDAI flares. Prior to 2000, the majority of person-time during pregnancy was unexposed to HCQ (63.2 person-years compared to 20.9 person-years exposed to HCQ). After 2000, standard of care practices changed, and the majority of patients during pregnancy, as well as the majority of patients during unexposed time and postpartum periods, were treated with HCQ (102.6 person-years compared to 34.1 person-years unexposed to HCQ during pregnancy).

The lack of consistency in the association for PGA flares compared to SELENA SLEDAI flares, particularly after the year 2000, may be due to the apparent lack of correlation between the two indices. Prior to 2000, the correlation between the two indices was 0.34 (Table 25). After 2000, the correlation decreased to 0.28.

Discussion

The present analysis from the Hopkins Lupus Cohort was one of the largest cohort studies to date to analyze the effect of pregnancy and the postpartum period on SLE disease flares. Including two disease activity indices, PGA and SELENA SLEDAI, in the same analytic cohort allowed us to compare how results may differ depending on the index used. We found that although the rates of flares differed slightly between the two indices, the hazard ratios for both exposures were similar. The results indicate that there is an increased incidence of flare during pregnancy compared to unexposed periods in women with SLE, and this association was seen across all models and sensitivity analytic cohorts. The results support what has previously been reported in the literature (7, 126, 127, 131). A previous analysis in this cohort by Clowse et al. (7) reported that among patients seen at least 6 months prior to pregnancy, 12.5% had high disease activity (PGA ≥2) compared to 21.3% of patients during pregnancy. Additionally, Petri and colleagues (126) found among 40 pregnant patients in this same cohort, rate of flare was greater during pregnancy than in non-pregnant controls, 1.6 flares per PY compared to 0.7 flares per PY, respectively. In a SLE cohort in the UK, Ruiz-Irastorza et al. (127) found that the rates of flare during pregnancy and a 6-week postpartum period were increased compared to non-pregnant, age-matched controls. The rate of flare during pregnancy was 0.082 per person-month compared to 0.039 per person-month in the control group. A study of 29 pregnancies in Hong Kong estimated a higher rate of flares during pregnancy compared to non-pregnant patients (0.08 per person-month compared to 0.04 per person-month, respectively) (131). However, our results are in contrast to other previous studies, which have found no evidence of an increased rate of flare during pregnancy (128, 132, 166), potentially due to differences in study design, sample size, or definition of flare.

Fewer studies have examined flares during the postpartum period, which is an important contribution of our study. Definitions of the postpartum period used previously in the literature have been inconsistent. In this same cohort, Petri et al. (126) reported a lower mean rate of flare per person-year after delivery than during pregnancy among 42 patients, with the rate of flare decreasing from 1.6 flares per PY during pregnancy to 0.7 per PY in the year after delivery. A study of 72 SLE patients in Argentina observed 19% of patients had flares during pregnancy, compared to 4% in the puerperium (51). Ruiz-Irastorza et al. (127) estimated a rate of flare during pregnancy of 0.08 per person-month, compared to

0.15 per person-month during the puerperium (defined as 8 weeks after pregnancy outcome), which decreased to 0.05 in the one year after puerperium. Age-matched controls in Ruiz-Irastorza's study had a lower rate of flare than both pregnancy and puerperium periods, with a mean incidence of 0.04 flares per person-month.

We observed no evidence of an increased rate of flare during the postpartum period compared to unexposed periods in crude, counting process Cox models, or stratified Cox models, with the incidence of flare in the 1-year postpartum period being similar to the incidence of flare during unexposed periods. However, this changed slightly in sensitivity analyses, where the incidence of flare based on PGA in unexposed periods decreased from 40.2 per 100 PY for the total cohort to 35.9 per 100 PY when the analysis was limited to only women with an observed pregnancy. A decrease in incidence in the unexposed period was also estimated when the incidence of flare was based on SELENA SLEDAI (47.3 per 100 PY in the total cohort compared to 39.5 per 100 PY when the analysis was limited to only women with an observed pregnancy). The decrease in the flare incidence in the sub-cohort resulted in the incidence rate ratio of flares in the postpartum period compared to unexposed periods to shift from a null association to a modestly increased association. This stresses the importance of the appropriate comparator group when analyzing flares during pregnancy and the postpartum periods.

Effect modification by medication use was observed. Among patients with no hydroxychloroquine use, there was an increased rate of flare during pregnancy compared to unexposed periods, but for patients taking hydroxychloroquine there was no evidence of an increased rate of flare during pregnancy. This is supported by a previous study in this cohort that found disease activity was increased during pregnancy for patients who discontinued hydroxychloroquine (7). Our results found that the hazard ratio of flare in pregnancy compared to unexposed periods when defined by PGA did not change when the cohort was limited to time since 2000. However, results from SELENA SLEDAI models suggest there is no evidence of an increased rate of flare during pregnancy compared to unexposed periods when time was restricted to 2000-2015. The observed differences between the two indices may be attributable to SELENA SLEDAI being an index with set values for disease activity that do not change over time, while a physician's perception of disease activity, as measured by PGA, can potentially change over time.

Additionally, we found that SELENA SLEDAI and PGA indices were not well correlated, with a correlation coefficient of 0.30 overall.

We included two variations of Cox models in our analysis: the stratified Cox model and the counting process Cox model. The stratified Cox model, unlike the counting process Cox model, takes into consideration the order in which flares occur, and different baseline hazards were allowed for the number of previous flares a patient had in the cohort (165). Given that a patient with no history of previous flares likely has a different baseline hazard of flare than a patient who has had multiple previous flares, a model that takes this into account seems more appropriate than an unadjusted model, such as the counting process Cox model. Therefore, we believe the results of the stratified Cox model are more representative of the true association of pregnancy and postpartum periods with flares than results from the counting process Cox models. A limitation of our study design was patients were censored in the model when the exposure changed. We accounted for this by creating a new ID variable when a patient's exposure changed, and included the original and new IDs in the model. However, this causes a patient's stratum for previous flares to be limited to the current exposure period, which may result in some residual confounding. Even so, we view this residual confounding to be preferable to the potentially biased estimates of the unadjusted counting process Cox models that do not account for or adjust for any previous flares.

The present analysis benefited from being able to use data from all women enrolled in the Hopkins Lupus Cohort, which allowed us to analyze more of the disease history of patients. Because all SLE patients may not be the most appropriate comparator group for women who become pregnant, we conducted a sensitivity analysis restricted to women with at least one observed pregnancy. The sensitivity analyses revealed that unexposed flare rates do change depending on the group of women analyzed – all women, women with a history of pregnancy, or women with an observed pregnancy. Additionally, we were limited by having to remove 77 patients from the analysis due to lack of unexposed period data for these patients, which resulted in removing 83 pregnancies. Sensitivity analyses including these patients did not reveal substantial changes to hazard ratios, but it is unknown how these patients differed during unexposed periods of time, which could influence our results. We also considered patients who had more than a one year gap between study visits to be considered lost to follow-up, although patients were

allowed to re-enter the analytic cohort when study visits resumed. This was done to include patients who were under routine care and to allow for an appropriate comparator PGA or SELENA SLEDAI score for the calculation of disease flare. The disease activity of these patients during unobserved periods is unknown, and if a gap in visits was due to remission of the disease, it is possible we underestimated the person-time for low disease activity periods for these patients. Additionally, flares captured in the analysis were based on flares observed while the patient was seen at the Lupus Center; therefore, we were unable to include flares that occurred while a patient was hospitalized and potentially underestimated the total number flares patients in the cohort experienced.

Conclusions

Our study supports and extends previous findings that the incidence of flare is increased during pregnancy compared to unexposed periods, and pregnant patients should continue to be closely observed during this time. Additionally, our analysis supported previous research that hydroxychloroquine should be continued to be used during pregnancy, as it appeared that among patients who used hydroxychloroquine, there was no evidence for an increased rate of flare during pregnancy compared to unexposed periods. We did not find evidence of an increased rate of flare during postpartum periods compared to unexposed periods, suggesting that patients may resume their standard rheumatologic care following pregnancy and do not need to be monitored as closely as they are during pregnancy.

Table 14. Demographics for SLE patients at baseline and pregnant women at time of first pregnancy in cohort in the Hopkins Lupus Cohort, 1987-2015.

	Total Cohort at Baseline n =1349	Pregnant Women at First Pregnancy in Cohort n =304
Race	n (%)	n (%)
White	656 (48.6%)	173 (56.9%)
Black	546 (40.5%)	102 (33.6%)
Other	147 (10.9%)	29 (9.5%)
	Median (IQR)	Median (IQR)
Age, years	30.6 (25.5-36.8)	29.4 (26.1-33.2)
Duration of SLE, years	2.0 (0.3-6.7)	4.8 (1.7-9.6)

Table 15. Pregnancy outcomes observed in the Hopkins Lupus Pregnancy Cohort, 1987-2015 (n=398 pregnancies in n=304 patients)

	n (%)
Live Birth	340 (85.4%)
Preterm birth[A]	98 (28.8%)
Small for gestational age[B]	83 (24.4%)
Large for gestational age[C]	12 (3.5%)
Fetal loss	46 (11.6%)
Miscarriage[D]	29 (63.0%)
Stillbirth[E]	17 (37.0%)
Elective termination	12 (3.0%)

[A]live birth at <37 weeks gestational age
[B]live birth with birth weight <10th percentile for gestational age
[C]live birth with birth weight <90th percentile for gestational age
[D]fetal loss at <20 weeks gestation
[E]fetal loss at ≥20 weeks gestation

Table 16. Number and crude incidence of flares during pregnancy, 1-year postpartum period, and unexposed periods of time for women with SLE in the Hopkins Lupus Cohort, 1987-2015 (n=1349).

	Flares	PY	Crude incidence per 100 PY	Crude IRR (95% CI)
PGA[A]				
All patients (n=1349)				
Unexposed	2246	5583.0	40.2	1.0 (ref)
Pregnancy	134	220.8	60.7	1.51 (1.27, 1.80)
Postpartum	148	370.9	39.9	0.99 (0.84, 1.17)
Patients with history of pregnancy or ≥1 observed pregnancy (n=999)				
Unexposed	1713	4355.9	39.3	1.0 (ref)
Pregnancy	134	220.8	60.7	1.54 (1.29, 1.84)
Postpartum	148	370.9	39.9	1.01 (0.86, 1.20)
Patients with ≥1 observed pregnancy in the cohort (n=304)				
Unexposed	642	1790.4	35.9	1.0 (ref)
Pregnancy	134	220.8	60.7	1.69 (1.40, 2.04)
Postpartum	148	370.9	39.9	1.11 (0.93, 1.33)
SELENA SLEDAI[B]				
All patients (n=1349)				
Unexposed	2641	5583.0	47.3	1.0 (ref)
Pregnancy	140	220.8	63.4	1.34 (1.13, 1.59)
Postpartum	170	370.9	45.8	0.97 (0.83, 1.13)
Patients with history of pregnancy or ≥1 observed pregnancy (n=999)				
Unexposed	1945	4355.9	44.7	1.0 (ref)
Pregnancy	140	220.8	63.4	1.42 (1.20, 1.69)
Postpartum	170	370.9	45.8	1.03 (0.88, 1.20)
Patients with ≥1 observed pregnancy in the cohort (n=304)				
Unexposed	708	1790.4	39.5	1.0 (ref)
Pregnancy	140	220.8	63.4	1.60 (1.34, 1.92)
Postpartum	170	370.9	45.8	1.16 (0.98, 1.37)

[A]flare defined as change in ≥1 from PGA score at previous visit
[B]flare defined as change in ≥4 from SELENA SLEDAI score at previous visit
CI: confidence interval; PGA: Physician Global Assessment of disease activity; PY: person-years; SLE: systemic lupus erythematosus; SLEDAI: SLE Disease Activity Index

Table 17. Hazard ratios of flares based on PGA[A] during pregnancy and 1-year postpartum period compared to unexposed periods for women with SLE in the Hopkins Lupus Cohort, 1987-2015 (n=1349).

	Counting Process Cox Proportional Hazard[B] HR (95% CI)	Stratified Cox[C] HR (95% CI)
All patients (n=1349)		
Unexposed	1.0 (ref)	1.0 (ref)
Pregnancy	1.44 (1.14, 1.75)	1.59 (1.27, 1.96)
Postpartum	0.94 (0.76, 1.13)	1.02 (0.83, 1.25)
Patients with history of pregnancy or ≥1 observed pregnancy (n=999)		
Unexposed	1.0 (ref)	1.0 (ref)
Pregnancy	1.49 (1.17, 1.86)	1.69 (1.36, 2.07)
Postpartum	0.98 (0.76, 1.21)	1.10 (0.91, 1.35)
Patients with ≥1 observed pregnancy in the cohort (n=304)		
Unexposed	1.0 (ref)	1.0 (ref)
Pregnancy	1.58 (1.24, 2.01)	1.88 (1.48, 2.49)
Postpartum	1.04 (0.80, 1.36)	1.24 (0.96, 1.66)

[A]flare defined as change in ≥1 from PGA score at previous visit

CI: confidence interval; HR: hazard ratio; PGA: Physician Global Assessment of disease activity; SLE: systemic lupus erythematosus

Table 18. Hazard ratios of flares based on SELENA SLEDAI[A] during pregnancy and 1-year postpartum period compared to unexposed periods for women with SLE in the Hopkins Lupus Cohort, 1987-2015 (n=1349).

	Counting Process Cox Proportional Hazard[B] HR (95% CI)	Stratified Cox[C] HR (95% CI)
All patients (n=1349)		
Unexposed	1.0 (ref)	1.0 (ref)
Pregnancy	1.30 (1.04, 1.62)	1.57 (1.25, 1.92)
Postpartum	0.93 (0.75, 1.12)	1.09 (0.89, 1.32)
Patients with history of pregnancy or ≥1 observed pregnancy (n=999)		
Unexposed	1.0 (ref)	1.0 (ref)
Pregnancy	1.38 (1.09, 1.71)	1.65 (1.30, 2.06)
Postpartum	0.99 (0.79, 1.21)	1.17 (0.95, 1.46)
Patients with ≥1 observed pregnancy in the cohort (n=304)		
Unexposed	1.0 (ref)	1.0 (ref)
Pregnancy	1.50 (1.13, 1.88)	1.82 (1.34, 2.38)
Postpartum	1.08 (0.86, 1.35)	1.32 (1.03, 1.69)

[A]flare defined as change in ≥4 from SELENA SLEDAI score at previous visit
CI: confidence interval; HR: hazard ratio; SLE: systemic lupus erythematosus; SLEDAI: SLE Disease Activity Index

Table 19. Modification by hydroxychloroquine of hazard ratios of flares based on PGA[A] during pregnancy and 1-year postpartum period compared to unexposed periods for women with SLE in the Hopkins Lupus Cohort, 1987-2015 (n=1349).

	Counting Process Cox Proportional Hazard[B]		Stratified Cox[C]	
	No HCQ Use	HCQ Use	No HCQ Use	HCQ Use
	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)
All patients (n=1349)				
Unexposed	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)
Pregnancy	1.74 (1.27, 2.29)	1.15 (0.81, 1.54)	1.83 (1.34, 2.45)	1.26 (0.88, 1.69)
Postpartum	0.93 (0.64, 1.23)	0.96 (0.69, 1.23)	0.98 (0.67, 1.31)	1.02 (0.72, 1.32)
Patients with history of pregnancy or ≥1 observed pregnancy (n=999)				
Unexposed	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)
Pregnancy	1.89 (1.39, 2.49)	1.17 (0.78, 1.56)	1.89 (1.46, 2.62)	1.32 (0.87, 1.77)
Postpartum	1.01 (0.70, 1.33)	0.97 (0.71, 1.28)	1.05 (0.73, 1.43)	1.05 (0.78, 1.40)
Patients with ≥1 observed pregnancy in the cohort (n=304)				
Unexposed	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)
Pregnancy	2.09 (1.48, 2.98)	1.22 (0.80, 1.69)	2.25 (1.58, 3.39)	1.45 (0.96, 2.09)
Postpartum	1.11 (0.76, 1.59)	1.05 (0.72, 1.43)	1.24 (0.84, 1.84)	1.20 (0.82, 1.65)

[A]flare defined as change in ≥1 from PGA score at previous visit

[B]Counting process Cox proportional hazards model assumes the order of the events of flares did not need to be taken into consideration

[C]Stratified Cox model is a conditional model that does not assume independence of multiple events of flares and allows different baseline hazards based on the number of previous flares a patient experienced

CI: confidence interval; HCQ: hydroxychloroquine; HR: hazard ratio; PGA: Physician Global Assessment of disease activity; SLE: systemic lupus erythematosus

Table 20. Modification by hydroxychloroquine of hazard ratios of flares based on SELENA SLEDAI[A] during pregnancy and 1-year postpartum period compared to unexposed periods for women with SLE in the Hopkins Lupus Cohort, 1987-2015 (n=1349).

	Counting Process Cox Proportional Hazard[B]		Stratified Cox[C]	
	No HCQ Use	HCQ Use	No HCQ Use	HCQ Use
	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)
All patients (n=1349)				
Unexposed	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)
Pregnancy	1.50 (1.11, 1.98)	1.14 (0.80, 1.52)	1.59 (1.17, 2.09)	1.35 (0.92, 1.81)
Postpartum	0.85 (0.60, 1.12)	1.01 (0.77, 1.27)	0.91 (0.64, 1.20)	1.13 (0.88, 1.44)
Patients with history of pregnancy or ≥1 observed pregnancy (n=999)				
Unexposed	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)
Pregnancy	1.67 (1.23, 2.23)	1.20 (0.83, 1.64)	1.71 (1.25, 2.28)	1.40 (0.97, 1.92)
Postpartum	0.95 (0.69, 1.27)	1.06 (0.80, 1.34)	1.00 (0.72, 1.34)	1.19 (0.90, 1.53)
Patients with ≥1 observed pregnancy in the cohort (n=304)				
Unexposed	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)
Pregnancy	1.97 (1.38, 2.76)	1.26 (0.83, 1.70)	2.09 (1.39, 2.97)	1.49 (0.92, 2.08)
Postpartum	1.10 (0.77, 1.55)	1.13 (0.83, 1.48)	1.18 (0.79, 1.69)	1.29 (0.93, 1.73)

[A]flare defined as change in ≥4 from SELENA SLEDAI score at previous visit
[B]Counting process Cox proportional hazards model assumes the order of the events of flares did not need to be taken into consideration
[C]Stratified Cox model is a conditional model that does not assume independence of multiple events of flares and allows different baseline hazards based on the number of previous flares a patient experienced
CI: confidence interval; HCQ: hydroxychloroquine; HR: hazard ratio; SLE: systemic lupus erythematosus; SLEDAI: SLE Disease Activity Index

Table 21. Hazard ratios of flares based on PGA[A] during pregnancy, 1-year postpartum period, and unexposed periods of time for women with SLE in the Hopkins Lupus Cohort, 2000-2015 (n=1073).

	Counting Process Cox Proportional Hazard[B] HR (95% CI)	Stratified Cox[C] HR (95% CI)
All patients (n=1073)		
Unexposed	1.0 (ref)	1.0 (ref)
Pregnancy	1.31 (0.93, 1.72)	1.47 (1.01, 2.02)
Postpartum	0.95 (0.68, 1.25)	1.05 (0.73, 1.43)
Patients with history of pregnancy or ≥1 observed pregnancy (n=787)		
Unexposed	1.0 (ref)	1.0 (ref)
Pregnancy	1.34 (0.96, 1.80)	1.57 (1.14, 2.13)
Postpartum	0.98 (0.69, 1.31)	1.13 (0.81, 1.52)
Patients with ≥1 observed pregnancy in the cohort (n=268)		
Unexposed	1.0 (ref)	1.0 (ref)
Pregnancy	1.47 (1.02, 2.03)	1.85 (1.24, 2.59)
Postpartum	1.11 (0.76, 1.55)	1.33 (0.90, 1.88)

[A]flare defined as change in ≥1 from PGA score at previous visit
[B]Counting process Cox proportional hazards model assumes the order of the events of flares did not need to be taken into consideration
[C]Stratified Cox model is a conditional model that does not assume independence of multiple events of flares and allows different baseline hazards based on the number of previous flares a patient experienced
CI: confidence interval; HR: hazard ratio; PGA: Physician Global Assessment of disease activity; SLE: systemic lupus erythematosus

Table 22. Hazard ratios of flares based on SELENA SLEDAI[A] during pregnancy, 1-year postpartum period, and unexposed periods of time for women with SLE in the Hopkins Lupus Cohort, 2000-2015 (n=1073).

	Counting Process Cox Proportional Hazard[B] HR (95% CI)	Stratified Cox[C] HR (95% CI)
All patients (n=1073)		
Unexposed	1.0 (ref)	1.0 (ref)
Pregnancy	1.09 (0.75, 1.46)	1.45 (0.99, 1.92)
Postpartum	0.99 (0.72, 1.26)	1.24 (0.92, 1.57)
Patients with history of pregnancy or ≥1 observed pregnancy (n=787)		
Unexposed	1.0 (ref)	1.0 (ref)
Pregnancy	1.18 (0.83, 1.57)	1.56 (1.12, 2.08)
Postpartum	1.07 (0.81, 1.34)	1.36 (1.03, 1.73)
Patients with ≥1 observed pregnancy in the cohort (n=268)		
Unexposed	1.0 (ref)	1.0 (ref)
Pregnancy	1.35 (0.91, 1.84)	1.77 (1.14, 2.43)
Postpartum	1.23 (0.88, 1.60)	1.58 (1.16, 2.11)

[A]flare defined as change in ≥4 from SELENA SLEDAI score at previous visit
[B]Counting process Cox proportional hazards model assumes the order of the events of flares did not need to be taken into consideration
[C]Stratified Cox model is a conditional model that does not assume independence of multiple events of flares and allows different baseline hazards based on the number of previous flares a patient experienced
CI: confidence interval; HR: hazard ratio; SLE: systemic lupus erythematosus; SLEDAI: SLE Disease Activity Index

Table 23. Modification by hydroxychloroquine of hazard ratios of flares based on PGA[A] during pregnancy and 1-year postpartum period compared to unexposed periods for women with SLE in the Hopkins Lupus Cohort, 2000-2015 (n=1073).

	Counting Process Cox Proportional Hazard[B]		Stratified Cox[C]	
	No HCQ Use	HCQ Use	No HCQ Use	HCQ Use
	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)
All patients (n=1073)				
Unexposed	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)
Pregnancy	1.68 (0.95, 2.64)	1.16 (0.77, 1.61)	1.75 (0.99, 2.91)	1.29 (0.87, 1.83)
Postpartum	0.97 (0.50, 1.63)	0.95 (0.62, 1.36)	1.02 (0.53, 1.75)	1.02 (0.69, 1.49)
Patients with history of pregnancy or ≥1 observed pregnancy (n=787)				
Unexposed	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)
Pregnancy	1.76 (0.93, 2.73)	1.18 (0.76, 1.66)	1.89 (1.08, 3.06)	1.35 (0.92, 2.00)
Postpartum	1.03 (0.49, 1.74)	0.96 (0.64, 1.38)	1.11 (0.52, 1.91)	1.06 (0.74, 1.66)
Patients with ≥1 observed pregnancy in the cohort (n=268)				
Unexposed	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)
Pregnancy	2.24 (1.15, 4.07)	1.25 (0.75, 1.84)	2.56 (1.24, 4.75)	1.49 (0.99, 2.41)
Postpartum	1.36 (0.59, 2.69)	1.05 (0.65, 1.54)	1.47 (0.64, 3.01)	1.20 (0.78, 1.87)

[A]flare defined as change in ≥1 from PGA score at previous visit

[B]Counting process Cox proportional hazards model assumes the order of the events of flares did not need to be taken into consideration

[C]Stratified Cox model is a conditional model that does not assume independence of multiple events of flares and allows different baseline hazards based on the number of previous flares a patient experienced

CI: confidence interval; HCQ: hydroxychloroquine; HR: hazard ratio; PGA: Physician Global Assessment of disease activity; SLE: systemic lupus erythematosus

Table 24. Modification by hydroxychloroquine of hazard ratios of flares based on SELENA SLEDAI[A] during pregnancy and 1-year postpartum period compared to unexposed periods for women with SLE in the Hopkins Lupus Cohort, 2000-2015 (n=1073).

	Counting Process Cox Proportional Hazard[B]		Stratified Cox[C]	
	No HCQ Use	HCQ Use	No HCQ Use	HCQ Use
	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)
All patients (n=1073)				
Unexposed	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)
Pregnancy	0.78 (0.29, 1.40)	1.20 (0.81, 1.68)	0.90 (0.38, 1.77)	1.48 (1.08, 2.26)
Postpartum	0.63 (0.28, 1.02)	1.12 (0.80, 1.46)	0.73 (0.34, 1.26)	1.30 (1.03, 1.86)
Patients with history of pregnancy or ≥1 observed pregnancy (n=787)				
Unexposed	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)
Pregnancy	0.92 (0.35, 1.68)	1.26 (0.86, 1.74)	1.02 (0.43, 2.07)	1.57 (1.14, 2.43)
Postpartum	0.78 (0.35, 1.31)	1.18 (0.85, 1.57)	0.85 (0.42, 1.65)	1.39 (1.10, 2.00)
Patients with ≥1 observed pregnancy in the cohort (n=268)				
Unexposed	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)
Pregnancy	1.30 (0.50, 2.57)	1.37 (0.88, 1.95)	1.34 (0.56, 2.96)	1.69 (1.13, 2.73)
Postpartum	1.04 (0.45, 1.89)	1.30 (0.95, 1.78)	1.14 (0.49, 2.23)	1.54 (1.23, 2.38)

[A]flare defined as change in ≥4 from SELENA SLEDAI score at previous visit
[B]Counting process Cox proportional hazards model assumes the order of the events of flares did not need to be taken into consideration
[C]Stratified Cox model is a conditional model that does not assume independence of multiple events of flares and allows different baseline hazards based on the number of previous flares a patient experienced
CI: confidence interval; HCQ: hydroxychloroquine; HR: hazard ratio; SLE: systemic lupus erythematosus; SLEDAI: SLE Disease Activity Index

Table 25. Correlation of flares defined by PGA[A] and SELENA-SLEDAI[B] for women with SLE in the Hopkins Lupus Cohort, 1987-2015 (n=1349).

	Pearson Correlation Coefficient
Overall	0.30
Prior to 2000	0.34
2000 and after	0.28

[A]flare defined as change in ≥1 from PGA score at previous visit
[B]flare defined as change in ≥4 from SELENA SLEDAI score at previous visit

CHAPTER 7: CONCLUSIONS

The objective of this dissertation was to further understand how SLE affects pregnancy, including gestational weight gain patterns and pregnancy outcomes, such as preterm birth and birth weight for gestational age z-score. Additionally, we sought advance the current knowledge about how pregnancy affects SLE disease activity, as measured by flares. The key findings of our study, the study's strengths and limitations, public health significance and direction of future research are summarized in the following section.

Summary of Findings

In the first specific aim, we estimated the proportion of pregnant women with SLE who met Institute of Medicine (IOM) guidelines for gestational weight gain (GWG) and determined correlates of adherence to IOM guidelines. Using a pre-pregnancy weight measured during the 12 months prior to pregnancy or in the first trimester and a final weight measurement closest to birth in the third trimester, we classified GWG as inadequate, adequate, or excessive based on pre-pregnancy BMI. We found that of 211 pregnancies, 34.1% of women had inadequate, 24.2% had adequate, and 41.7% had excessive weight gain. In descriptive analyses, differences in IOM adherence were observed by pre-pregnancy BMI, race, elevated creatinine during pregnancy, and pre-pregnancy blood pressure. In logistic regression models, stepwise selection determined continuous pre-pregnancy BMI and maternal education level to be predictors of inadequate and excessive weight gain. With each 1 kg/m^2 increase in pre-pregnancy BMI, the odds of inadequate weight gain and excessive weight gain both increased 12%. Compared to patients with a greater than college education, patients with a high school education had approximately three times the odds of inadequate weight gain and twice the odds of excessive weight gain.

In the second specific aim, we determined the proportion of pregnant women with SLE meeting the American Heart Association (AHA) guidelines for ideal cardiovascular health, and estimated the effects of pre-conceptional cardiovascular health on pregnancy outcomes. Body mass index (BMI), total

cholesterol and blood pressure in the most recent clinic visit in the one-year prior to conception or 1st trimester were used to classify cardiovascular health according to AHA criteria (ideal, intermediate or poor health). Pregnancy outcomes of interest included preterm birth (delivery prior to 37 completed weeks' gestation), gestational age at birth, small for gestational age (SGA; less than the 10th percentile of weight for gestational age) and birth weight-for-gestational age z-score. Among 309 singleton live births to 261 SLE patients, there were 95 preterm births (31%), and of the 293 pregnancies with birth weights, 18% were SGA. Ideal BMI (underweight/normal weight), ideal total cholesterol (<200 mg/dL), and ideal blood pressure (<120/<80 mm Hg) were observed in 56%, 86%, and 51% of pregnancies, respectively. Among SLE patients, overweight was associated with increased odds of preterm birth [Odds Ratio (OR): 1.38; 95% CI: 0.70, 2.71] and decreased odds of SGA (OR: 0.26; 95% CI: 0.11, 0.63) compared to underweight/normal weight, adjusted for race and prednisone use. In models adjusted for race and anti-malarial use, intermediate/poor total cholesterol was associated with increased odds of preterm birth (OR: 1.91; 95% CI: 0.96, 3.79). Intermediate/poor blood pressure was associated with decreased gestational age at birth (β: -0.96; 95% CI: -1.62, -0.29).

The third specific aim estimated the effect of pregnancy and one-year postpartum period on flares in women SLE. Using data available on all women aged 15-45 in the Hopkins Lupus Cohort, we calculated disease flares during periods of pregnancy, a one-year postpartum period, and during unexposed periods when patients were neither pregnancy nor in a postpartum period. SLE disease flares were classified according to two indices: Physician Global Assessment of disease activity (PGA) and SELENA SLE Disease Activity Index (SLEDAI). A flare based on the PGA index was defined as a change in PGA ≥1 from previous visit, and a flare based on the SELENA SLEDAI index was defined as a change in SELENA SLEDAI ≥4 from the previous visit. The hazard ratios of flares during pregnancy compared to unexposed periods and postpartum compared to unexposed periods were estimated using two variations of Cox models. The first model was the standard counting process Cox proportional hazards model, which assumed that the order of the events of flares did not need to be taken into consideration. The second model was a stratified Cox model, a conditional model that did not assume independence of multiple events of flare, and instead included a stratum for the time interval number was included in the model so a patient was not at risk for a second flare without having experienced a previous flare. The

analysis included 1349 SLE patients, of which n=304 patients had n=398 pregnancies. In counting process Cox models, an increased rate of flares during pregnancy compared to unexposed periods was estimated in counting process Cox models for PGA (HR: 1.44; 95% CI: 1.14, 1.75) and SELENA SLEDAI flare (HR: 1.30; 95% CI: 1.04, 1.62). There was no evidence of increased rate of flares during postpartum compared to unexposed periods. In stratified Cox models, the increased rate of flare during pregnancy persisted for PGA (HR: 1.59; 95% CI: 1.27, 1.96) and SELENA SLEDAI flare (HR: 1.09; 95% CI: 0.89, 1.32). Similar to counting process Cox models, there was no evidence of increased rate of flares during postpartum compared to unexposed periods. Hydroxychloroquine use was found to be an effect modifier in the association of pregnancy and flares. When flares were measured by PGA, counting process Cox models estimated the HR of flares in pregnancy compared to unexposed periods to be 1.74 (95% CI: 1.27, 2.29) for patients with no hydroxychloroquine use and 1.15 (95% CI: 0.81, 1.54) for patients with hydroxychloroquine use (likelihood ratio p-value: 0.02). This modification by hydroxychloroquine use was also observed in stratified Cox models. When flares were measured by SELENA SLEDAI, counting process Cox models estimated the HR of flares in pregnancy compared to unexposed periods to be 1.50 (95% CI: 1.11, 1.98) for patients with no hydroxychloroquine use and 1.14 (95% CI: 0.80, 1.52) for patients with hydroxychloroquine use (likelihood ratio p-value=0.12). There was no evidence in any models that hydroxychloroquine use modified the association of flares in the postpartum period compared to unexposed periods. We included two variations of Cox models in our analysis: the stratified Cox model and the counting process Cox model. Given that the stratified Cox model takes into consideration the order in which flares occur and allows different baseline hazards for the number of previous flares a patient had in the cohort (165), we concluded that the results of the stratified Cox model are more representative of the true association of pregnancy and postpartum periods with flares than results from the counting process Cox models.

Study Limitations

Our study had several limitations. In Aims 1 and 2, our study suffered from small sample sizes. In Aim 1, we were unable to further explore the interaction of BMI with demographic and clinical features due to insufficient power. Previous research has found that factors associated with non-adherence, such

as race, education and certain co-morbidities vary by BMI group (141), but we were unable to further explore these interactions in our analysis. In Aim 2, the small sample size and low frequency of large for gestational age births did not allow us to explore the effect of cardiovascular health on this birth outcome. While the cohort is larger than other SLE pregnancy cohorts, the modest sample size did not provide sufficient power to detect small differences in outcomes.

Another limitation of our analysis, particularly in Aims 1 and 2, is the possibility of selection bias due to clinical and demographics differences in pregnancies that were excluded from analyses due to missing data. It is possible that our results in Aims 1 and 2 would differ if excluded patients had been retained in the analysis. In Aim 1, maternal weight at the beginning and end of pregnancy were not available for all live births in the cohort. Live births excluded from the analysis (210 of 421 singleton live births) were more frequently to mothers with a high school education and a pregnancy outcome date prior to 1999. Additionally, excluded pregnancies were to mothers with a lower frequency of anti-malarial use during pregnancy and shorter disease duration. In Aim 2, cardiovascular data were not available for all live births in the cohort. A greater proportion of live births excluded from the analysis due to missing cardiovascular health data (112 of 421 singleton live births) were to mothers who were black and had a pregnancy outcome data prior to 1999, compared to the final analysis population. Additionally, excluded births were to mothers who had shorter disease duration, lower frequency of anti-malarial use during pregnancy and lower frequency of low C3/C4. In Aim 3, we excluded 77 pregnancies in patients who did not have any unexposed follow-up time. While our sensitivity analysis that included these patients found no major differences in the estimated hazards ratios, it is unknown what disease activity these patients had when they were not pregnant and if the missingness of their data was due to their disease activity. In Aim 3, we also considered patients who had more than a one year gap between study visits to be considered lost to follow-up, although patients were allowed to re-enter the analytic cohort when study visits resumed. This was done to include patients who were under routine care and to allow for an appropriate comparator PGA or SELENA SLEDAI score for the calculation of disease flare. The disease activity of these patients during unobserved periods is unknown, and if a gap in visits was due to remission of the disease, it is possible we underestimated the person-time for low disease activity periods for these patients.

Third, data were unavailable on the four remaining AHA cardiovascular metrics (glucose, physical activity, diet, and cigarette smoking); therefore, we were unable to assess the combined effects of cardiovascular risk factors in Aim 2. Additional data on physical activity and diet would have also benefited Aim 1 by allowing us to understand how physical activity and diet can help further explain differences in weight gain patterns in this patient population.

Fourth, the data were collected at a single academic center. While this is favorable with respects to consistency in the treatment of patients and data collection, the cohort described in this analysis may not be representative of all SLE patients and our results may not be generalizable to all SLE patients.

Finally, although we used prospectively collected data from a longitudinal cohort and were able to adjust for potential confounders in our analyses, there remains the possibility of unmeasured confounding that could affect our results. This concern is common in all observational studies, though, and is not limited to this study.

Study Strengths

Although the sample sizes in Aims 1 and 2 were modest, this study reports one of the largest cohorts of pregnant women with SLE, and it is the first study to analyze gestational weight gain patterns in SLE, as well as the first to examine the AHA's guidelines for cardiovascular health in patients with SLE prior to conception.

The Hopkins Lupus Cohort is a longitudinal cohort study, with data prospectively collected by a single rheumatologist since 1987. The prospective collection of data provided us with clinically recorded weights, rather than having to rely on self-report of pre-pregnancy weight of total gestational weight gain by the patient, which has been found to often be inaccurately remembered at the time of delivery (145). Additionally, the longitudinal nature of the cohort allowed for weights to be measured at multiple times during pregnancy, which allowed for weight gain trajectories to be constructed in Aim 1.

The analysis utilized various statistical methods to determine the incidence of flare during pregnancy and the postpartum period compared to unexposed periods. We demonstrated that results were similar in both counting process and stratified Cox models. Our results support the importance of continuing to monitor SLE patients for flares during pregnancy and suggest that there is no increased rate

of flare during the one year postpartum period. Additionally, we were able to utilize two accepted and validated clinical indices of disease activity, PGA and SELENA SLEDAI, in our analysis, which allowed us to compare results across different indices.

Public Health Implications

The appropriate amount of weight gained during pregnancy has great implications for the infant: gaining too much weight during pregnancy has been shown to be associated with delivering large for gestational age or macrosomic (>4000 g) infants (73-89), while insufficient weight gain is associated with the delivery of a small for gestational age infant (74, 75, 78-84, 90). The adverse effect of gaining too much weight during pregnancy continues throughout childhood, with excessive GWG being associated with childhood obesity (94, 139, 140). Gestational weight gain also has implications for preterm birth. There appears to be a U-shaped association of GWG with preterm birth, with modification by pre-pregnancy BMI (10, 91-94). Among women who are underweight according to their pre-pregnancy BMI, less than ideal GWG is associated with an increased risk of preterm birth, and this association weakens as pre-pregnancy BMI increases. More than ideal GWG may be associated with preterm birth in women of all pre-pregnancy BMI categories (9, 10). Our analysis in Aim 1 found that only 24% of SLE patients gained an adequate amount of weight, which could have an effect on pregnancy outcomes in this population. Additionally, our findings in Aim 1 identified maternal education and pre-pregnancy BMI as correlates of adherence to GWG guidelines. This suggests interventions in this patient population may benefit from being targeted toward patients with increased BMI and lower maternal education.

The findings of Aim 2 have important implications for SLE patients during pregnancy. Of particular interest in our analysis was the apparent inverse association of obesity but the increased risk of preterm birth in overweight patients. This suggests that efforts to normalize maternal weight prior to pregnancy may improve pregnancy outcomes. Previous studies have found that among patients with SLE, pregnancy increases the risk of future major cardiovascular events and a poor pregnancy outcome increases the risk cardiovascular mortality (164). Interventions to improve the cardiovascular health of patients prior to pregnancy would improve pregnancy outcomes, as well as benefit the long-term health of SLE patients.

The results from Aim 3 support previous findings that the incidence of flare is increased during pregnancy compared to unexposed periods. However, in our sensitivity analysis limited to time since the year 2000, we observed no evidence of increased flares defined by SELENA SLEDAI during pregnancy, which may indicate that previous recommendations of increased monitoring of pregnant SLE patients have been successful in reducing the rate of flare during pregnancy. We did not find evidence of an increased rate of flare during postpartum periods compared to unexposed periods, suggesting that patients may resume their standard rheumatologic care following pregnancy and do not need to be monitored as closely as they are during pregnancy. Additionally, our analysis supported previous research that hydroxychloroquine should be continued to be used during pregnancy, by finding the association of flare during pregnancy compared to unexposed periods to be modified by hydroxychloroquine use. Based on previous findings that high disease activity during pregnancy is associated with poor pregnancy outcomes (7), understanding how disease activity changes during pregnancy will be important to improve pregnancy outcomes in women with SLE.

Direction of Future Research

As described previously, our study was limited by sample size, as well as the lack of several important cardiovascular health metrics. Further investigations of our research topic in a diverse and global SLE cohort would increase statistical power and improve generalizability of study results. Specifically, we believe the following areas are important for future research:

1) Collect additional measures of cardiovascular health

   The American Heart Association 2020 Impact Goals included the development of the concept of "ideal cardiovascular health," focuses on primary prevention and is composed of seven modifiable cardiovascular metrics: health factors (glucose, cholesterol, and blood pressure) and health behaviors (body mass index, physical activity, diet, and cigarette smoking) (95). Meeting these metrics for ideal cardiovascular health is associated with a lower risk of cardiovascular disease and lower cardiovascular and all-cause mortality rates. Data were unavailable in our study on glucose, physical activity, diet, and current cigarette smoking. Availability of these data would provide a more complete

picture of how pre-cardiovascular health impacts pregnancy outcomes by analyzing the combined effects of all seven cardiovascular risk factors. Additionally, having a further understanding of SLE patients who are able to maintain ideal cardiovascular health will be important in order to develop future targeted treatments. Data on physical activity and diet would also benefit our understanding of the patterns of physical activity and diet during pregnancy for SLE patients, and the implications of each on gestational weight gain patterns in SLE.

2) Understand appropriateness of IOM guidelines for SLE patients

The IOM formed a committee to update the recommendations for GWG. Guidelines were revised to reflect the recognized need for weight gain recommendations to be specific to a woman's pre-pregnancy BMI. Although the 2009 committee was not intended to develop GWG guidelines for specific diseases or conditions, a noticeable gap in the literature was the availability of data on the weight gain patterns in patients with SLE. It has yet to be determined if the IOM guidelines for weight gain in the general population are appropriate for women with SLE. Our study found that the majority of SLE patients do not meet IOM guidelines for GWG, and future studies are necessary to determine if pregnancy outcomes in women with SLE are improved when IOM guidelines for gestational weight gain are met.

APPENDIX 1. 1997 UPDATE OF THE 1982 AMERICAN COLLEGE OF RHEUMATOLOGY (ACR) CRITERIA FOR CLASSIFICATION OF SLE (12, 13)

Criteria	Description
1. Malar Rash	Fixed erythema, flat or raised, over the malar eminences, tending to spare the nasolabial folds
2. Discoid Rash	Erythematous raised patches with adherent keratotic scaling and follicular plugging; atrophic scarring may occur in older lesions
3. Photosensitivity	Skin rash as a result of unusual reaction to sunlight, by patient history or physician observation
4. Oral ulcers	Oral or nasopharyngeal ulceration, usually painless, observed by physician
5. Nonerosive Arthritis	Involving 2 or more peripheral joints, characterized by tenderness, swelling, or effusion
6. Pleuritis or Pericarditis	a. Pleuritis (convincing history of pleuritic pain or rubbing heard by a physician or evidence of pleural effusion) ***OR*** b. Pericarditis (documented by electrocardigram or rub or evidence of pericardial effusion)
7. Kidney Disorder	a. Persistent proteinuria > 0.5 grams per day or > than 3+ if quantitation not performed ***OR*** b. Cellular casts (may be red cell, hemoglobin, granular, tubular, or mixed)
8. Neurologic Disorder	a. Seizures in the absence of offending drugs or known metabolic derangements (e.g., uremia, ketoacidosis, or electrolyte imbalance) ***OR*** b. Psychosis in the absence of offending drugs or known metabolic derangements (e.g., uremia, ketoacidosis, or electrolyte imbalance)
9. Hematologic Disorder	a. Hemolytic anemia with reticulocytosis ***OR*** b. Leukopenia (< 4,000/mm^3 on ≥ 2 occasions) ***OR*** c. Lyphopenia (< 1,500/ mm^3 on ≥ 2 occasions) ***OR*** d. Thrombocytopenia (<100,000/ mm^3 in the absence of offending drugs)
10. Immunologic Disorder	a. Anti-DNA (antibody to native DNA in abnormal titer) ***OR*** b. Anti-Sm (presence of antibody to Sm nuclear antigen) ***OR*** c. Positive finding of antiphospholipid antibodies on: i. an abnormal serum level of IgG or IgM anticardiolipin antibodies, ii. a positive test result for lupus anticoagulant using a standard method, or iii. a false-positive test result for at least 6 months confirmed by Treponema pallidum immobilization or fluorescent treponemal antibody absorption test
11. Positive Antinuclear Antibody	An abnormal titer of antinuclear antibody by immunofluorescence or an equivalent assay at any point in time and in the absence of drugs

*Hochberg, M. C. (1997). "Updating the American college of rheumatology revised criteria for the classification of systemic lupus erythematosus." Arthritis & Rheumatism **40**(9): 1725-1725.*

APPENDIX 2. SYSTEMIC LUPUS ERYTHEMATOSUS DISEASE ACTIVITY INDEX (SLEDAI) SELENA MODIFICATION

Check box: if descriptor is present at the time of visit or in the preceding 10 days.

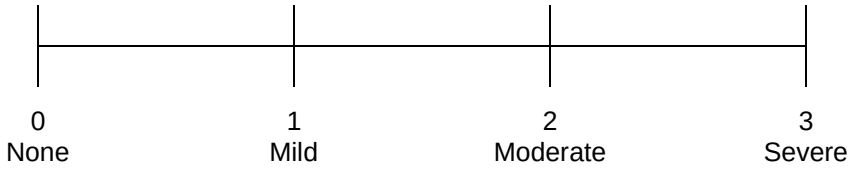
Weight	Check if Present	Descriptor	Definition
8	□	Seizure	Recent onset (last 10 days). Exclude metabolic, infectious or drug cause.
8	□	Psychosis	Altered ability to function in normal activity due to severe disturbance in the perception of reality. Include hallucinations, incoherence, marked loose associations, impoverished thought content, marked illogical thinking, bizarre, disorganized, or catatonic behavior. Excluded uremia and drug causes.
8	□	Organic brain syndrome	Altered mental function with impaired orientation, memory or other intelligent function, with rapid onset fluctuating clinical features. Include clouding of consciousness with reduced capacity to focus, and inability to sustain attention to environment, plus at least two of the following: perceptual disturbance, incoherent speech, insomnia or daytime drowsiness, or increased or decreased psychomotor activity. Exclude metabolic, infectious or drug causes.
8	□	Visual disturbance	Retinal changes of SLE. Include cytoid bodies, retinal hemorrhages, serious exodate or hemorrhages in the choroids, or optic neuritis. Exclude hypertension, infection, or drug causes.
8	□	Cranial nerve disorder	New onset of sensory or motor neuropathy involving cranial nerves.
8	□	Lupus headache	Severe persistent headache: may be migrainous, but must be nonresponsive to narcotic analgesia
8	□	CVA	New onset of cerebrovascular accident(s). Exclude arteriosclerosis.
8	□	Vasculitis	Ulceration, gangrene, tender finger nodules, periungual, infarction, splinter hemorrhages, or biopsy or angiogram proof of vasculitis
4	□	Arthritis	More than 2 joints with pain and signs of inflammation (i.e., tenderness, swelling or effusion).
4	□	Myositis	Proximal muscle aching/weakness, associated with elevated creatine phosphokinase/aldolase or electromyogram changes or a biopsy showing myositis.
4	□	Urinary casts	Heme-granular or red blood cell casts
4	□	Hematuria	>5 red blood cells/high power field. Exclude stone, infection or other cause.
4	□	Proteinuria	>0.5 gm/24 hours. New onset or recent increase of more than 0.5 gm/24 hours.
4	□	Pyuria	>5 white blood cells/high power field. Exclude infection.
2	□	New Rash	New onset or recurrence of inflammatory type rash.
2	□	Alopecia	New onset or recurrence of abnormal, patchy or diffuse loss of hair.
2	□	Mucosal ulcers	New onset or recurrence of oral or nasal ulcerations
2	□	Pleurisy	Pleuritic chest pain with pleural rub or effusion, or pleural thickening.
2	□	Pericarditis	Pericardial pain with at least 1 of the following: rub, effusion, or electrocardiogram confirmation.
2	□	Low complement	Decrease in CH50, C3 or C4 below the lower limit of normal for testing laboratory.

2	□	Increased DNA binding	>25% binding by Farr assay or above normal range for testing laboratory.
1	□	Fever	>38◦C. Exclude infectious cause.
1	□	Thrombocytopenia	<100,000 platelets/mm^3.
1	□	Leukopenia	<3,000 white blood cells/mm^3. Exclude drug causes.
_____ TOTAL SCORE (Sum of weights next to descriptors marked present)			

Petri M, Kim MY, Kalunian KC, et al. Combined oral contraceptives in women with systemic lupus erythematosus. N Engl J Med 2005;353:2550-8. (117)

APPENDIX 3. PHYSICIAN'S GLOBAL ASSESSMENT OF DISEASE ACTIVITY (PGA)

How do you assess your patient's current disease activity?



Petri M, Kim MY, Kalunian KC, et al. Combined oral contraceptives in women with systemic lupus erythematosus. N Engl J Med 2005;353:2550-8. (117)

APPENDIX 4. SUPPLEMENTAL TABLES FOR CHAPTER IV: GESTATIONAL WEIGHT GAIN IN PREGNANT WOMEN WITH SYSTEMIC LUPUS ERYTHEMATOSUS

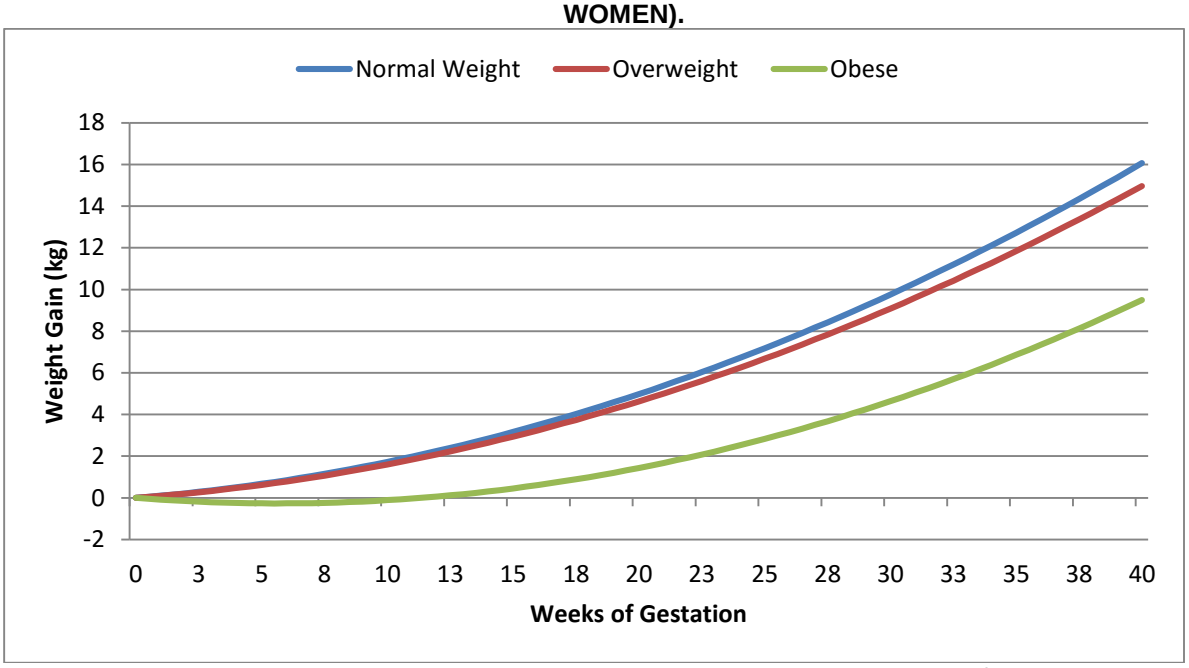
APPENDIX 4.1. UNIVARIATE LOGISTIC REGRESSION MODELS FOR CLINICAL AND DEMOGRAPHICS FACTORS ASSOCIATED WITH GESTATIONAL WEIGHT GAIN IN WOMEN WITH SLE IN THE HOPKINS LUPUS PREGNANCY COHORT (N=211).

		Inadequate Weight Gain	Excessive Weight Gain
	n	OR (95% CI)	OR (95% CI)
Race			
Black	65	2.46 (1.12, 5.41)	1.08 (0.50, 2.37)
White	146	1.0	1.0
Age			
>30	110	1.16 (0.55, 2.45)	1.19 (0.60, 2.37)
≤30	101	1.0	1.0
Education			
HS Education (≤12 years)	57	3.85 (1.35, 10.99)	2.00 (0.73, 5.55)
College (13-16 years)	100	1.96 (0.77, 4.97)	1.37 (0.61, 3.09)
Greater than College (>16 years)	54	1.0	1.0
Duration of SLE			
>5 years	110	0.97 (0.48, 1.96)	0.79 (0.40, 1.55)
≤5 years	101	1.0	1.0
Prednisone use during pregnancy			
Yes	102	1.39 (0.68, 2.86)	1.26 (0.61, 2.59)
No	109	1.0	1.0
Prednisone Use ≥15 mg/day During Pregnancy among Prednisone Users (n=102)			
Yes	48	1.35 (0.44, 4.18)	1.48 (0.51, 4.26)
No	54	1.0	1.0
Anti-malarial use during pregnancy			
Yes	152	0.86 (0.39, 1.91)	0.66 (0.30, 1.47)
No	59	1.0	1.0
Immunosuppressants use during pregnancy			
Yes	37	1.13 (0.41, 3.17)	1.73 (0.66, 4.55)
No	174	1.0	1.0
High PGA (≥2) during pregnancy			
Yes	36	1.13 (0.40, 3.18)	1.62 (0.64, 4.06)
No	175	1.0	1.0
SDI at Conception			
≥1	79	2.00 (0.93, 4.28)	1.66 (0.80, 3.46)
0	132	1.0	1.0
Renal involvement during pregnancy			
Yes	60	1.20 (0.53, 2.72)	1.23 (0.56, 2.67)
No	151	1.0	1.0
Low C3 during pregnancy			
Yes	51	0.61 (0.28, 1.32)	0.38 (0.17, 0.83)
No	160	1.0	1.0
Low C4 during pregnancy			
Yes	76	0.73 (0.36, 1.49)	0.51 (0.25, 1.06)
No	135	1.0	1.0
Anti-dsDNA during pregnancy			
Yes	83	1.47 (0.70, 3.07)	1.10 (0.53, 2.27)
No	128	1.0	1.0
Pre-pregnancy blood pressure			
Intermediate/poor	106	2.65 (1.28, 5.47)	2.40 (1.16, 4.95)

Ideal	105	1.0	1.0
Pre-pregnancy cholesterol			
Ideal	178	1.0	1.0
Intermediate/poor	22	1.24 (0.41, 3.74)	1.03 (0.32, 3.30)
Pre-pregnancy BMI			
Under/normal weight (≤24.9)	121	1.0	1.0
Overweight (25.0 - 29.9)	47	1.52 (0.58, 4.00)	2.48 (1.05, 5.82)
Obese (≥30)	43	5.85 (1.56, 21.91)	6.81 (1.86, 25.00)
Age at conception, years	211	0.99 (0.92, 1.07)	0.98 (0.91, 1.05)
Disease duration, years	211	0.97 (0.92, 1.03)	0.96 (0.91, 1.02)
Highest PGA during pregnancy	211	1.15 (0.67, 1.96)	1.40 (0.84, 2.32)
SDI at conception	211	1.43 (1.00, 2.04)	1.35 (0.96, 1.89)
Highest daily prednisone dose during pregnancy, mg	211	1.02 (0.99, 1.05)	1.00 (0.98, 1.03)
Highest daily prednisone dose during pregnancy among prednisone users, mg	102	1.01 (0.98, 1.06)	0.99 (0.96, 1.03)
Pre-pregnancy BMI, kg/m^2	211	1.13 (1.04, 1.22)	1.12 (1.04, 1.21)

Abbreviations: BMI, body mass index; C3, complement 3; C4, complement 4; HS, high school; LAI, Lupus Activity Index; OR, odds ratios; PGA: Physician Global Assessment of Disease Activity; SDI: SLICC/ACR Damage Index

APPENDIX 4.2. MEAN PREDICTED CHANGE IN WEIGHT DURING PREGNANCY FROM MIXED EFFECTS MODELS, STRATIFIED BY PRE-PREGNANCY BMI (EXCLUDING UNDERWEIGHT WOMEN).



[A]Mean weight change = 4.4778 + 0.3973(gestational age) + 0.0076(gestational age^2) + 0.6414(overweight) + 3.3288(obese) – 0.0268(gestational age x overweight) – 0.1647(gestational age x obese) – 0.0004 (gestational age^2 x overweight) + 0.0006 (gestational age^2 x obese)

APPENDIX 5. SUPPLEMENTAL TABLES FOR CHAPTER V: PRE-CONCEPTIONAL CARDIOVASCULAR HEALTH AND PREGNANCY OUTCOMES IN WOMEN WITH SYSTEMIC LUPUS ERYTHEMATOSUS

APPENDIX 5.1. DEMOGRAPHICS STRATIFIED BY PRE-PREGNANCY OR 1ST TRIMESTER VISIT (N=309)

	Pre-Pregnancy Visit (n=195)	1st Trimester Visit (n=114)	
	n (%)	**n (%)**	**Fisher p-value**
Race			
White	108 (55%)	76 (67%)	0.1
Black	64 (32%)	29 (25%)	
Other	23 (12%)	9 (8%)	
Education			
HS Education (≤12 years)	64 (33%)	37 (32%)	0.1
College (13-16 years)	82 (42%)	59 (52%)	
Greater than College (>16 years)	49 (25%)	18 (16%)	
Infant birth date			
Prior to Jan 1999	51 (26%)	66 (58%)	<0.0001
Jan 1999 – February 2015	144 (74%)	48 (42%)	
Medication use during pregnancy[A]			
Anti-malarial	134 (69%)	50 (44%)	<0.0001
Immunosuppressant	38 (19%)	10 (9%)	0.01
Prednisone	92 (47%)	68 (60%)	0.04
Prednisone ≥7.5 mg/day	62 (32%)	54 (47%)	0.01
Prednisone ≥7.5 mg/day among prednisone users (n=160)	62 (67%)	54 (79%)	0.1
Clinical characteristics during pregnancy[A]			
Renal involvement (LAI)	49 (25%)	30 (26%)	0.9
Elevated serum creatinine (>1)	17 (9%)	7 (6%)	0.5
High PGA during pregnancy (PGA ≥2)	26 (13%)	23 (20%)	0.1
Low C3 during pregnancy	39 (20%)	35 (31%)	0.04
Low C4 during pregnancy	64 (33%)	42 (37%)	0.5
Anti-dsDNA	70 (36%)	45 (39%)	0.5
	Mean (SD)	**Mean (SD)**	**ANOVA p-value**
Age at conception, years	30.2 (4.9)	29.4 (5.0)	0.2
Disease duration, years	7.4 (5.2)	4.6 (5.0)	<0.0001
Highest PGA during pregnancy (scale: 0-3)	0.9 (0.7)	1.1 (0.7)	0.01
Highest daily prednisone dose during pregnancy, mg	7.9 (13.0)	11.4 (14.0)	0.03
BMI, kg/m^2	26.2 (6.1)	25.5 (6.1)	0.4
Total cholesterol	168.8 (36.1)	157.0 (30.4)	0.01
Systolic blood pressure	117.5 (15.2)	115.3 (14.5)	0.2
Diastolic blood pressure	73.1 (10.9)	69.7 (8.7)	0.005

[A]categories not mutually exclusive; women can be in multiple categories, therefore, percentages add up to more than 100%

Abbreviations: BMI, body mass index; C3, complement 3; C4, complement 4; HS, high school; LAI, Lupus Activity Index; OR, odds ratios; PGA: Physician Global Assessment of Disease Activity; SDI: SLICC/ACR Damage Index

APPENDIX 5.2. LIVE BIRTH OUTCOMES STRATIFIED BY PRE-PREGNANCY OR 1ST TRIMESTER VISIT (N=309)

	Pre-Pregnancy Visit (n=195)	1st Trimester Visit (n=114)	
	n (%)	**n (%)**	**Fisher p-value**
Small for gestational age (n=293)	29 (16%)	24 (22%)	0.2
Large for gestational age (n=293)	9 (5%)	3 (3%)	0.5
Preterm birth	56 (29%)	39 (34%)	0.4
	Mean (SD)	**Mean (SD)**	**ANOVA p-value**
Gestational age at birth, weeks	36.9 (3.0)	36.9 (3.3)	1.0
Birth weight percentile (n=293)	37.5 (27.0)	32.8 (24.8)	0.1
Birth weight z-score (n=293)	-0.42 (0.92)	-0.62 (0.92)	0.07
Birth weight (g) (n=293)	2859.0 (762.4)	2793.7 (750.2)	0.5

APPENDIX 5.3. PRE-CONCEPTIONAL CARDIOVASCULAR HEALTH ACCORDING TO AHA CRITERIA STRATIFIED BY PRE-PREGNANCY OR 1ST TRIMESTER VISIT

		Poor Health	Intermediate Health	Ideal Health	Fisher p-value
Body mass index[A] (n=291)					
Pre-Pregnancy Visit (n=193)	n (%)	43 (22%)	44 (23%)	106 (55%)	0.5
1st Trimester Visit (n=98)	n (%)	16 (16%)	25 (26%)	57 (58%)	
Total cholesterol[B] (n=275)					
Pre-Pregnancy Visit (n=192)	n (%)	8 (4%)	24 (13%)	160 (83%)	0.1
1st Trimester Visit (n=83)	n (%)	0 (0%)	8 (10%)	75 (90%)	
Blood pressure[C] (n=309)					
Pre-Pregnancy Visit (n=195)	n (%)	25 (13%)	78 (40%)	92 (47%)	0.2
1st Trimester Visit (n=114)	n (%)	9 (8%)	39 (34%)	66 (58%)	

[A] Body mass index: (1) poor health: ≥30 kg/m^2; (2) intermediate health: 25-29.9 kg/m^2; (3) ideal health: <25 kg/m^2

[B] Total cholesterol: (1) poor health: ≥240 mg/dL; (2) intermediate health: 200–239 mg/dL or treated to goal; (3) ideal health: <200 mg/Dl

[C] Blood pressure: (1) poor health: Systolic ≥140 or Diastolic ≥90 mm Hg; (2) intermediate health: Systolic 120–139 or Diastolic 80–89 mm Hg or treated to goal; (3) ideal health: <120/<80 mm Hg

APPENDIX 5.4. DISTRIBUTION OF PRETERM BIRTH, SGA AND LGA BY PRE-CONCEPTIONAL CARDIOVASCULAR HEALTH AMONG PATIENTS WITH PRE-PREGNANCY VISITS ONLY (N=195)

	Preterm birth	SGA	LGA
Body mass index			
Ideal health (under/normal weight; <25 kg/m^2)	31 of 106 (29%)	19 of 100 (19%)	4 of 100 (5%)
Intermediate health (overweight; 25-29.9 kg/m^2)	17 of 44 (39%)	2 of 43 (5%)	3 of 43 (7%)
Poor health (obese; ≥30 kg/m^2)	8 of 43 (19%)	7 of 40 (18%)	2 of 40 (6%)
ANOVA p-value	*0.1*	*0.06*	*0.7*
Total cholesterol			
Ideal health (<200 mg/dL)	42 of 160 (26%)	26 of 151 (17%)	6 of 151 (4%)
Intermediate health (200–239 mg/dL or treated to goal)	8 of 24 (33%)	2 of 23 (9%)	3 of 23 (13%)
Poor health (≥240 mg/dL)	6 of 8 (75%)	1 of 8 (13%)	0 of 8 (0%)
ANOVA p-value	*0.01*	*0.8*	*0.1*
Blood pressure			
Ideal health (<120/<80 mm Hg)	23 of 92 (25%)	15 of 87 (17%)	7 of 87 (8%)
Intermediate health (Systolic 120–139 or Diastolic 80–89 mm Hg or treated to goal)	25 of 78 (32%)	13 of 75 (17%)	2 of 75 (3%)
Poor health (Systolic ≥140 or Diastolic ≥90 mm Hg)	8 of 25 (32%)	1 of 23 (4%)	0 of 23 (0%)
ANOVA p-value	*0.5*	*0.3*	*0.2*

LGA: large for gestational age; SGA: small for gestational age

APPENDIX 5.5. MEAN GESTATIONAL AGE AND BIRTH WEIGHT Z-SCORES BY PRE-CONCEPTIONAL CARDIOVASCULAR HEALTH, WITH ANOVA TESTS FOR DIFFERENCES IN MEANS, AMONG PATIENTS WITH PRE-PREGNANCY VISITS ONLY (N=195)

	Gestational Age Mean Weeks (SD)	Birth Weight Z-Score Mean (SD)
Body mass index		
Ideal health (under/normal weight; <25 kg/m^2)	36.6 (3.3)	-0.49 (0.90)
Intermediate health (overweight; 25-29.9 kg/m^2)	36.7 (2.7)	-0.20 (0.81)
Poor health (obese; ≥30 kg/m^2)	37.6 (2.6)	-0.42 (1.06)
ANOVA p-value	*0.2*	*0.2*
Total cholesterol		
Ideal health (<200 mg/dL)	36.9 (3.1)	-0.42 (0.94)
Intermediate health (200–239 mg/dL or treated to goal)	37.1 (2.3)	-0.27 (0.96)
Poor health (≥240 mg/dL)	34.9 (3.9)	-0.53 (0.60)
ANOVA p-value	*0.2*	*0.7*
Blood pressure		
Ideal health (<120/<80 mm Hg)	37.4 (2.7)	-0.39 (0.98)
Intermediate health (Systolic 120–139 or Diastolic 80–89 mm Hg or treated to goal)	36.4 (3.2)	-0.43 (0.95)
Poor health (Systolic ≥140 or Diastolic ≥90 mm Hg)	36.4 (3.4)	-0.49 (0.54)
ANOVA p-value	*0.08*	*0.9*

APPENDIX 5.6. MULTIVARIABLE LOGISTIC REGRESSION MODELS FOR ASSOCIATION OF PRE-CONCEPTIONAL CARDIOVASCULAR HEALTH AND PREGNANCY OUTCOMES IN SLE, AMONG PATIENTS WITH PRE-PREGNANCY VISITS ONLY (N=195).

	Preterm Birth		SGA	
	OR (95% CI)	AOR (95% CI)	OR (95% CI)	AOR (95% CI)
Body Mass Index[A]				
Ideal Health (under/normal weight)	1.0	1.0	1.0	1.0
Intermediate Health (overweight)	1.52 (0.72, 3.17)	1.43 (0.62, 3.33)[D]	0.24 (0.06, 0.92)	0.21 (0.05, 0.82)[D]
Poor Health (obese)	0.55 (0.24, 1.28)	0.52 (0.20, 1.38)[D]	0.81 (0.30, 2.23)	0.69 (0.23, 2.05)[D]
Total Cholesterol[B]				
Ideal Health	1.0	1.0	1.0	1.0
Intermediate/Poor Health	2.20 (1.01, 4.79)	2.02 (0.87, 4.70)[D]	0.40 (0.10, 1.59)	0.21 (0.03, 1.46)[D]
		1.83 (0.83, 4.04)[E]		0.46 (0.12, 1.81)[E]
		1.76 (0.77, 4.01)[F]		0.28 (0.05, 1.68)[F]
Blood Pressure[C]				
Ideal Health	1.0	1.0	1.0	1.0
Intermediate/Poor Health	1.40 (0.74, 2.62)	1.23 (0.65, 2.32)[G]	0.72 (0.34, 1.57)	0.72 (0.32, 1.59)[G]
Continuous variables				
BMI, kg/m^2	0.97 (0.92, 1.02)	0.96 (0.90, 1.02)[D]	0.99 (0.92, 1.06)	0.97 (0.89, 1.06)[D]
Total cholesterol, per 10 mg/dL change	1.11 (1.02, 1.21)	1.10 (1.00, 1.21)[D]	0.87 (0.75, 1.02)	0.83 (0.70, 0.99)[D]
		1.07 (0.99, 1.16)[E]		0.88 (0.75, 1.03)[E]
		1.09 (0.99, 1.19)[F]		0.84 (0.70, 1.00)[F]
Systolic blood pressure, per 10 mmHg change	1.15 (0.95, 1.40)	1.11 (0.91, 1.36)[G]	0.72 (0.52, 1.00)	0.72 (0.52, 0.99)[G]
Diastolic blood pressure, per 10 mmHg change	1.33 (1.01, 1.75)	1.27 (0.95, 1.69)[G]	0.78 (0.54, 1.13)	0.78 (0.54, 1.13)[G]

[A] Body mass index: (1) poor health: ≥30 kg/m^2; (2) intermediate health: 25-29.9 kg/m^2; (3) ideal health: <25 kg/m^2

[B] Total cholesterol: (1) poor health: ≥240 mg/dL; (2) intermediate health: 200–239 mg/dL or treated to goal; (3) ideal health: <200 mg/Dl

[C] Blood pressure: (1) poor health: Systolic ≥140 or Diastolic ≥90 mm Hg; (2) intermediate health: Systolic 120–139 or Diastolic 80–89 mm Hg or treated to goal; (3) ideal health: <120/<80 mm Hg

[D] Adjusted for race (black vs. non-black) and prednisone use ever during pregnancy

[E] Adjusted for race (black vs. non-black) and anti-malarial use ever during pregnancy

[F] Adjusted for race (black vs. non-black), prednisone use ever during pregnancy, and anti-malarial use ever during pregnancy

[G] Adjusted for race (black vs. non-black) and renal involvement during pregnancy (Renal LAI ≥1)

APPENDIX 5.7. MULTIVARIABLE LINEAR REGRESSION MODELS FOR ASSOCIATION OF PRE-CONCEPTIONAL CARDIOVASCULAR HEALTH AND PREGNANCY OUTCOMES IN SLE, AMONG PATIENTS WITH PRE-PREGNANCY VISITS ONLY (N=195).

	Gestational Age		Birthweight for Gestational Age Z-Score	
	B (95% CI)	Adjusted β (95% CI)	B (95% CI)	Adjusted β (95% CI)
Body Mass Index[A]				
Ideal Health (under/normal weight)	Ref	Ref	Ref	Ref
Intermediate Health (overweight)	0.11 (-0.96, 1.18)	0.20 (-0.93, 1.23)[D]	0.29 (-0.04, 0.62)	0.35 (0.03, 0.68)[D]
Poor Health (obese)	1.01 (-0.06, 2.09)	0.89 (-0.16, 1.94)[D]	0.07 (-0.27, 0.41)	0.11 (-0.22, 0.45)[D]
Total Cholesterol[B]				
Ideal Health	Ref	Ref	Ref	Ref
Intermediate/Poor Health	-0.41 (-1.57, 0.76)	-0.20 (-1.31, 0.92)[D]	0.08 (-0.28, 0.44)	0.10 (-0.25, 0.46)[D]
		-0.18 (1.36, 0.99)[E]		0.01 (-0.35, 0.37)[E]
		-0.07 (-1.20, 1.06))[F]		0.01 (-0.34, 0.37)[F]
Blood Pressure[C]				
Ideal Health	Ref	Ref	Ref	Ref
Intermediate/Poor Health	-0.97 (-1.82, -0.13)	-0.86 (-1.72, -0.003)[G]	-0.05 (-0.32, 0.22)	0.01 (-0.26, 0.28)[G]
Continuous variables				
BMI, kg/m^2	0.07 (-0.003, 0.14)	0.07 (-0.001, 0.14)[D]	0.01 (-0.01, 0.03)	0.01 (-0.01, 0.04)[D]
Total cholesterol, mg/dL	-0.07 (-0.19, 0.05)	-0.05 (-0.17, 0.06)[D]	0.01 (-0.03, 0.05)	0.02 (-0.02, 0.05)[D]
		-0.05 (-0.17, 0.08)[E]		0.004 (-0.03, 0.04)[E]
		-0.04 (-0.15, 0.08)[F]		0.01 (-0.03, 0.04)[F]
Systolic BP, mm Hg	-0.39 (-0.67, -0.12)	-0.35 (-0.64, -0.07)[G]	0.03 (-0.06, 0.12)	0.05 (-0.04, 0.14)[G]
Diastolic BP, mm Hg	-0.57 (-0.95, -0.18)	-0.51 (-0.91, -0.11)[G]	-0.03 (-0.15, 0.10)	0.01 (-0.12, 0.13)[G]

[A] Body mass index: (1) poor health: ≥30 kg/m^2; (2) intermediate health: 25-29.9 kg/m^2; (3) ideal health: <25 kg/m^2

[B] Total cholesterol: (1) poor health: ≥240 mg/dL; (2) intermediate health: 200–239 mg/dL or treated to goal; (3) ideal health: <200 mg/Dl

[C] Blood pressure: (1) poor health: Systolic ≥140 or Diastolic ≥90 mm Hg; (2) intermediate health: Systolic 120–139 or Diastolic 80–89 mm Hg or treated to goal; (3) ideal health: <120/<80 mm Hg

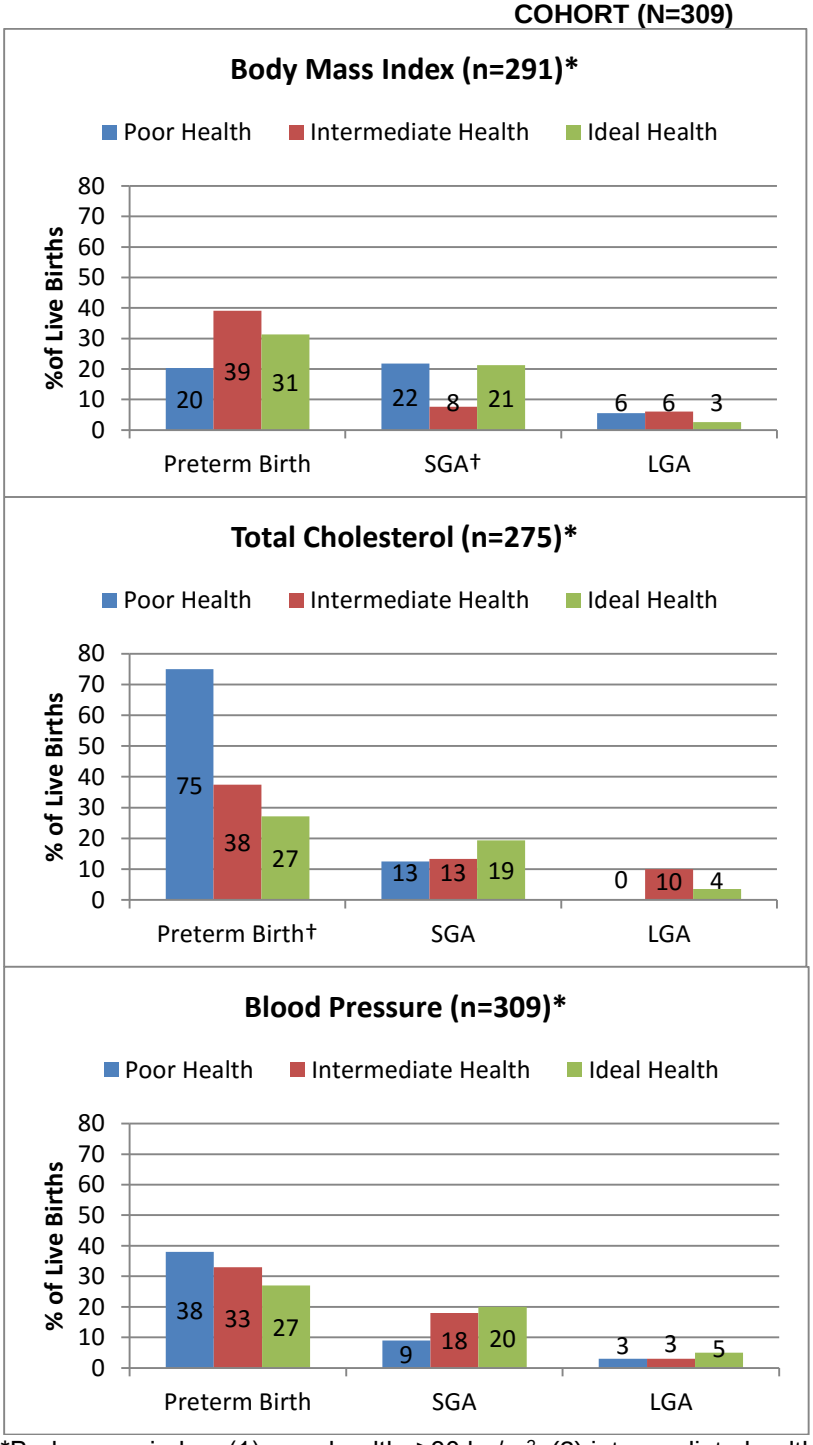
[D] Adjusted for race (black vs. non-black) and prednisone use ever during pregnancy

[E] Adjusted for race (black vs. non-black) and anti-malarial use ever during pregnancy

[F] Adjusted for race (black vs. non-black), prednisone use ever during pregnancy, and anti-malarial use ever during pregnancy

[G] Adjusted for race (black vs. non-black) and renal involvement during pregnancy (Renal LAI ≥1)

APPENDIX 5.8. PREVALENCE OF PRETERM BIRTH, SGA AND LGA AMONG LIVE BIRTHS BY PRE-CONCEPTIONAL CARDIOVASCULAR HEALTH IN THE HOPKINS LUPUS PREGNANCY COHORT (N=309)



*Body mass index: (1) poor health: ≥30 kg/m^2; (2) intermediate health: 25-29.9 kg/m^2; (3) ideal health: <25 kg/m^2; Total cholesterol: (1) poor health: ≥240 mg/dL; (2) intermediate health: 200–239 mg/dL or treated to goal; (3) ideal health: <200 mg/dL; Blood pressure: (1) poor health: Systolic ≥140 or Diastolic ≥90 mm Hg; (2) intermediate health: Systolic 120–139 or Diastolic 80–89 mm Hg or treated to goal; (3) ideal health: <120/<80 mm Hg

†Fisher's exact p-value <0.05

APPENDIX 6. SUPPLEMENTAL TABLES FOR CHAPTER VI: EFFECT OF PREGNANCY ON DISEASE FLARES IN PATIENTS WITH SYSTEMIC LUPUS ERYTHEMATOSUS

APPENDIX 6.1. MODIFICATION BY PREDNISONE OF HAZARD RATIOS OF FLARES BASED ON PGA[A] DURING PREGNANCY AND 1-YEAR POSTPARTUM PERIOD COMPARED TO UNEXPOSED PERIODS FOR WOMEN WITH SLE IN THE HOPKINS LUPUS COHORT, 1987-2015 (N=1349).

	Counting Process Cox[B]		Stratified Cox[C]	
	No Prednisone Use HR (95% CI)	Prednisone Use HR (95% CI)	No Prednisone Use HR (95% CI)	Prednisone Use HR (95% CI)
All patients (n=1349)				
Unexposed	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)
Pregnancy	1.54 (1.09, 2.10)	1.48 (1.13, 1.93)	1.54 (1.09, 2.12)	1.51 (1.15, 1.97)
Postpartum	0.96 (0.65, 1.32)	0.94 (0.73, 1.17)	0.97 (0.65, 1.36)	0.96 (0.75, 1.21)
Patients with history of pregnancy or ≥1 observed pregnancy (n=999)				
Unexposed	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)
Pregnancy	1.63 (1.14, 2.18)	1.50 (1.11, 1.93)	1.69 (1.18, 2.29)	1.53 (1.14, 2.03)
Postpartum	1.02 (0.69, 1.44)	0.95 (0.73, 1.21)	1.03 (0.69, 1.45)	0.98 (0.74, 1.25)
Patients with ≥1 observed pregnancy in the cohort (n=304)				
Unexposed	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)
Pregnancy	1.76 (1.18, 2.57)	1.53 (1.09, 2.09)	1.82 (1.20, 2.72)	1.57 (1.11, 2.24)
Postpartum	1.13 (0.72, 1.63)	0.98 (0.72, 1.30)	1.14 (0.71, 1.66)	1.02 (0.76, 1.41)

[A]flare defined as change in ≥1 from PGA score at previous visit

[B]Counting process Cox proportional hazards model assumes the order of the events of flares did not need to be taken into consideration

[C]Stratified Cox model is a conditional model that does not assume independence of multiple events of flares and allows different baseline hazards based on the number of previous flares a patient experienced

CI: confidence interval; HR: hazard ratio; PGA: Physician Global Assessment of disease activity; SLE: systemic lupus erythematosus

APPENDIX 6.2. MODIFICATION BY PREDNISONE OF HAZARD RATIOS OF FLARES BASED ON SELENA SLEDAI[A] DURING PREGNANCY AND 1-YEAR POSTPARTUM PERIOD COMPARED TO UNEXPOSED PERIODS FOR WOMEN WITH SLE IN THE HOPKINS LUPUS COHORT, 1987-2015 (N=1349).

	Counting Process Cox[B]		Stratified Cox[C]	
	No Prednisone Use HR (95% CI)	Prednisone Use HR (95% CI)	No Prednisone Use HR (95% CI)	Prednisone Use HR (95% CI)
All patients (n=1349)				
Unexposed	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)
Pregnancy	1.62 (1.09, 2.19)	1.30 (0.95, 1.66)	1.68 (1.15, 2.31)	1.41 (1.03, 1.81)
Postpartum	0.95 (0.65, 1.33)	0.95 (0.74, 1.19)	1.00 (0.67, 1.38)	1.01 (0.78, 1.28)
Patients with history of pregnancy or ≥1 observed pregnancy (n=999)				
Unexposed	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)
Pregnancy	1.69 (1.16, 2.37)	1.35 (0.98, 1.75)	1.74 (1.16, 2.43)	1.45 (1.03, 1.94)
Postpartum	1.00 (0.67, 1.41)	0.99 (0.77, 1.25)	1.04 (0.69, 1.46)	1.06 (0.82, 1.36)
Patients with ≥1 observed pregnancy in the cohort (n=304)				
Unexposed	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)
Pregnancy	1.84 (1.19, 2.65)	1.38 (0.99, 1.85)	1.91 (1.23, 2.81)	1.44 (0.98, 2.01)
Postpartum	1.09 (0.70, 1.59)	1.02 (0.77, 1.31)	1.14 (0.75, 1.75)	1.09 (0.78, 1.46)

[A]flare defined as change in ≥4 from SELENA SLEDAI score at previous visit
[B]Counting process Cox proportional hazards model assumes the order of the events of flares did not need to be taken into consideration
[C]Stratified Cox model is a conditional model that does not assume independence of multiple events of flares and allows different baseline hazards based on the number of previous flares a patient experienced
CI: confidence interval; HR: hazard ratio; SLE: systemic lupus erythematosus; SLEDAI: SLE Disease Activity Index

APPENDIX 6.3. NUMBER AND CRUDE INCIDENCE OF FLARES DURING PREGNANCY, 1-YEAR POSTPARTUM PERIOD, AND UNEXPOSED PERIODS OF TIME FOR WOMEN WITH SLE IN THE HOPKINS LUPUS COHORT, 2000-2015 (N=1073).

	Flares	PY	Crude incidence per 100 PY	Crude IRR (95% CI)
PGA[A]				
All patients (n=1073)				
Unexposed	1373	4015.0	34.2	1.0 (ref)
Pregnancy	61	136.7	44.6	1.31 (1.01, 1.69)
Postpartum	70	219.5	31.9	0.93 (0.73, 1.19)
Patients with history of pregnancy or ≥1 observed pregnancy (n=787)				
Unexposed	1036	3071.3	33.7	1.0 (ref)
Pregnancy	61	136.7	44.6	1.32 (1.02, 1.71)
Postpartum	70	219.5	31.9	0.95 (0.74, 1.20)
Patients with ≥1 observed pregnancy in the cohort (n=268)				
Unexposed	395	1301.9	30.3	1.0 (ref)
Pregnancy	61	136.7	44.6	1.47 (1.12, 1.93)
Postpartum	70	219.5	31.9	1.05 (0.82, 1.36)
SELENA SLEDAI[B]				
All patients (n=1073)				
Unexposed	1720	4015.0	42.8	1.0 (ref)
Pregnancy	65	136.7	47.6	1.11 (0.87, 1.42)
Postpartum	95	219.5	43.3	1.01 (0.82, 1.24)
Patients with history of pregnancy or ≥1 observed pregnancy (n=787)				
Unexposed	1220	4015.0	39.7	1.0 (ref)
Pregnancy	65	136.7	47.6	1.20 (0.93, 1.54)
Postpartum	95	219.5	43.3	1.09 (0.88, 1.34)
Patients with ≥1 observed pregnancy in the cohort (n=268)				
Unexposed	461	4015.0	34.8	1.0 (ref)
Pregnancy	65	136.7	47.6	1.37 (1.05, 1.77)
Postpartum	95	219.5	43.3	1.24 (1.00, 1.55)

[A]flare defined as change in ≥1 from PGA score at previous visit
[B]flare defined as change in ≥4 from SELENA SLEDAI score at previous visit
CI: confidence interval; IRR: incidence rate ratio; PGA: Physician Global Assessment of disease activity; PY: person-years; SLE: systemic lupus erythematosus; SLEDAI: SLE Disease Activity Index

APPENDIX 6.4. NUMBER AND CRUDE INCIDENCE OF PGA[A] FLARES DURING PREGNANCY, 1-YEAR POSTPARTUM PERIOD, AND UNEXPOSED PERIODS OF TIME FOR WOMEN WITH SLE IN THE HOPKINS LUPUS COHORT STRATIFIED BY HYDROXYCHLOROQUINE USE, 1987-2015 (N=1349).

	No HCQ Use				HCQ Use			
	Flares	PY	Crude incidence per 100 PY	Crude IRR (95% CI)	Flares	PY	Crude incidence per 100 PY	Crude IRR (95% CI)
Prior to 2000								
All patients (n=550)								
Unexposed	417	767.6	54.3	1.0 (ref)	456	800.1	57.0	1.0 (ref)
Pregnancy	60	63.2	94.9	1.75 (1.33, 2.29)	13	20.9	62.1	1.09 (0.63, 1.89)
Postpartum	52	104.8	49.6	0.91 (0.68, 1.22)	26	46.5	55.9	0.98 (0.66, 1.46)
Patients with history of pregnancy or ≥1 observed pregnancy (n=439)								
Unexposed	292	594.2	49.1	1.0 (ref)	385	691.5	55.7	1.0 (ref)
Pregnancy	60	63.2	94.9	1.93 (1.46, 2.55)	13	20.9	62.1	1.12 (0.64, 1.94)
Postpartum	52	104.8	49.6	1.01 (0.75, 1.36)	26	46.5	55.9	1.00 (0.68, 1.49)
Patients with ≥1 observed pregnancy in the cohort (n=161)								
Unexposed	111	232.0	47.9	1.0 (ref)	136	270.2	50.3	1.0 (ref)
Pregnancy	60	63.2	94.9	1.98 (1.45, 2.72)	13	20.9	62.1	1.23 (0.70, 2.18)
Postpartum	52	104.8	49.6	1.04 (0.75, 1.44)	26	46.5	55.9	1.11 (0.73, 1.69)
2000 and after								
All patients (n=1073)								
Unexposed	371	973.5	38.1	1.0 (ref)	1002	3041.4	32.9	1.0 (ref)
Pregnancy	22	34.1	64.5	1.69 (1.10, 2.60)	39	102.6	38.0	1.15 (0.84, 1.59)
Postpartum	21	53.8	39.0	1.02 (0.66, 1.60)	49	165.7	29.6	0.90 (0.67, 1.20)
Patients with history of pregnancy or ≥1 observed pregnancy (n=787)								
Unexposed	262	718.9	36.4	1.0 (ref)	774	2352.4	32.9	1.0 (ref)
Pregnancy	22	34.1	64.5	1.77 (1.15, 2.74)	39	102.6	38.0	1.16 (0.84, 1.59)
Postpartum	21	53.8	39.0	1.07 (0.69, 1.67)	49	165.7	29.6	0.90 (0.67, 1.20)
Patients with ≥1 observed pregnancy in the cohort (n=268)								
Unexposed	83	300.9	27.6	1.0 (ref)	312	1023.6	30.5	1.0 (ref)
Pregnancy	22	34.1	64.5	2.34 (1.46, 3.74)	39	102.6	38.0	1.25 (0.89, 1.74)
Postpartum	21	53.8	39.0	1.41 (0.88, 2.28)	49	165.7	29.6	0.97 (0.72, 1.31)

[A]flare defined as change in ≥1 from PGA score at previous visit

APPENDIX 6.5. NUMBER AND CRUDE INCIDENCE OF SELENA-SLEDAI[A] FLARES DURING PREGNANCY, 1-YEAR POSTPARTUM PERIOD, AND UNEXPOSED PERIODS OF TIME FOR WOMEN WITH SLE IN THE HOPKINS LUPUS COHORT STRATIFIED BY HYDROXYCHLOROQUINE USE, 1987-2015 (N=1349).

	No HCQ Use				HCQ Use			
	Flares	PY	Crude incidence per 100 PY	Crude IRR (95% CI)	Flares	PY	Crude incidence per 100 PY	Crude IRR (95% CI)
Prior to 2000								
All patients (n=550)								
Unexposed	449	767.6	58.5	1.0 (ref)	472	800.1	59.0	1.0 (ref)
Pregnancy	64	63.2	101.2	1.73 (1.33, 2.25)	11	20.9	52.6	0.89 (0.49, 1.62)
Postpartum	54	104.8	51.5	0.88 (0.66, 1.17)	21	46.5	45.2	0.77 (0.49, 1.19)
Patients with history of pregnancy or ≥1 observed pregnancy (n=439)								
Unexposed	325	594.2	54.7	1.0 (ref)	400	691.5	57.8	1.0 (ref)
Pregnancy	64	63.2	101.2	1.85 (1.42, 2.42)	11	20.9	52.6	0.91 (0.50, 1.65)
Postpartum	54	104.8	51.5	0.94 (0.71, 1.26)	21	46.5	45.2	0.78 (0.50, 1.21)
Patients with ≥1 observed pregnancy in the cohort (n=161)								
Unexposed	106	232.0	45.7	1.0 (ref)	141	270.2	52.2	1.0 (ref)
Pregnancy	64	63.2	101.2	2.22 (1.62, 3.02)	11	20.9	52.6	1.01 (0.55, 1.86)
Postpartum	54	104.8	51.5	1.13 (0.81, 1.57)	21	46.5	45.2	0.87 (0.55, 1.37)
2000 and after								
All patients (n=1073)								
Unexposed	427	973.5	43.9	1.0 (ref)	1293	3041.4	42.5	1.0 (ref)
Pregnancy	12	34.1	35.2	0.80 (0.45, 1.42)	53	102.6	51.7	1.22 (0.92, 1.60)
Postpartum	16	53.8	29.7	0.68 (0.41, 1.12)	79	165.7	47.7	1.12 (0.89, 1.41)
Patients with history of pregnancy or ≥1 observed pregnancy (n=787)								
Unexposed	263	718.9	36.6	1.0 (ref)	957	2352.4	40.7	1.0 (ref)
Pregnancy	12	34.1	35.2	0.96 (0.54, 1.72)	53	102.6	51.7	1.27 (0.96, 1.67)
Postpartum	16	53.8	29.7	0.81 (0.49, 1.35)	79	165.7	47.7	1.17 (0.93, 1.47)
Patients with ≥1 observed pregnancy in the cohort (n=268)								
Unexposed	81	300.9	26.9	1.0 (ref)	380	1023.6	37.1	1.0 (ref)
Pregnancy	12	34.1	35.2	1.31 (0.71, 2.40)	53	102.6	51.7	1.39 (1.04, 1.86)
Postpartum	16	53.8	29.7	1.10 (0.65, 1.89)	79	165.7	47.7	1.28 (1.01, 1.63)

[A]flare defined as change in ≥4 from SELENA SLEDAI score at previous visit

APPENDIX 6.6. NUMBER AND CRUDE INCIDENCE OF FLARES DURING PREGNANCY, 1-YEAR POSTPARTUM PERIOD, AND UNEXPOSED PERIODS OF TIME FOR WOMEN WITH SLE IN THE HOPKINS LUPUS COHORT, 1987-2015 (N=1426).

	Flares	PY	Crude incidence per 100 PY	Crude IRR (95% CI)
PGA[A]				
All patients (n=1426)				
Unexposed	2246	5583.0	40.2	1.0 (ref)
Pregnancy	150	252.6	59.4	1.48 (1.25, 1.74)
Postpartum	160	431.6	37.1	0.92 (0.78, 1.08)
Patients with history of pregnancy or ≥1 observed pregnancy (n=1076)				
Unexposed	1713	4357.2	39.3	1.0 (ref)
Pregnancy	150	252.6	59.4	1.51 (1.28, 1.79)
Postpartum	160	431.6	37.1	0.94 (0.80, 1.11)
Patients with ≥1 observed pregnancy in the cohort (n=381)				
Unexposed	642	1791.8	35.8	1.0 (ref)
Pregnancy	150	252.6	59.4	1.66 (1.39, 1.98)
Postpartum	160	431.6	37.1	1.03 (0.87, 1.23)
SELENA SLEDAI[B]				
All patients (n=1426)				
Unexposed	2641	5583.0	47.3	1.0 (ref)
Pregnancy	166	252.6	65.7	1.39 (1.19, 1.63)
Postpartum	181	431.6	41.9	0.89 (0.76, 1.03)
Patients with history of pregnancy or ≥1 observed pregnancy (n=1076)				
Unexposed	1945	4357.2	44.6	1.0 (ref)
Pregnancy	166	252.6	65.7	1.47 (1.26, 1.73)
Postpartum	181	431.6	41.9	0.94 (0.81, 1.09)
Patients with ≥1 observed pregnancy in the cohort (n=381)				
Unexposed	708	1791.8	39.5	1.0 (ref)
Pregnancy	166	252.6	65.7	1.66 (1.40, 1.97)
Postpartum	181	431.6	41.9	1.06 (0.90, 1.25)

[A]flare defined as change in ≥1 from PGA score at previous visit
[B]flare defined as change in ≥4 from SELENA SLEDAI score at previous visit
CI: confidence interval; IRR: incidence rate ratio; PGA: Physician Global Assessment of disease activity; PY: person-years; SLE: systemic lupus erythematosus; SLEDAI: SLE Disease Activity Index

APPENDIX 6.7 HAZARD RATIOS OF FLARES BASED ON PGA[A] DURING PREGNANCY AND 1-YEAR POSTPARTUM PERIOD COMPARED TO UNEXPOSED PERIODS FOR WOMEN WITH SLE IN THE HOPKINS LUPUS COHORT, 1987-2015 (N=1426).

	Counting Process Cox[B] HR (95% CI)	Stratified Cox[C] HR (95% CI)
All patients (n=1426)		
Unexposed	1.0 (ref)	1.0 (ref)
Pregnancy	1.38 (1.13, 1.67)	1.52 (1.25, 1.83)
Postpartum	0.86 (0.70, 1.03)	0.94 (0.76, 1.15)
Patients with history of pregnancy or ≥1 observed pregnancy (n=1076)		
Unexposed	1.0 (ref)	1.0 (ref)
Pregnancy	1.44 (1.15, 1.73)	1.62 (1.30, 1.98)
Postpartum	0.90 (0.72, 1.09)	1.01 (0.80, 1.23)
Patients with ≥1 observed pregnancy in the cohort (n=381)		
Unexposed	1.0 (ref)	1.0 (ref)
Pregnancy	1.53 (1.20, 1.95)	1.82 (1.43, 2.33)
Postpartum	0.96 (0.77, 1.22)	1.15 (0.94, 1.52)

[A]flare defined as change in ≥1 from PGA score at previous visit

[B]Counting process Cox proportional hazards model assumes the order of the events of flares did not need to be taken into consideration

[C]Stratified Cox model is a conditional model that does not assume independence of multiple events of flares and allows different baseline hazards based on the number of previous flares a patient experienced

CI: confidence interval; HR: hazard ratio; PGA: Physician Global Assessment of disease activity; SLE: systemic lupus erythematosus

APPENDIX 6.8. HAZARD RATIOS OF FLARES BASED ON SELENA SLEDAI[A] DURING PREGNANCY AND 1-YEAR POSTPARTUM PERIOD COMPARED TO UNEXPOSED PERIODS FOR WOMEN WITH SLE IN THE HOPKINS LUPUS COHORT, 1987-2015 (N=1426).

	Counting Process Cox[B] HR (95% CI)	Stratified Cox[C] HR (95% CI)
All patients (n=1426)		
Unexposed	1.0 (ref)	1.0 (ref)
Pregnancy	1.34 (1.08, 1.63)	1.60 (1.30, 1.96)
Postpartum	0.85 (0.68, 1.01)	1.02 (0.81, 1.24)
Patients with history of pregnancy or ≥1 observed pregnancy (n=1076)		
Unexposed	1.0 (ref)	1.0 (ref)
Pregnancy	1.42 (1.12, 1.71)	1.67 (1.33, 2.07)
Postpartum	0.90 (0.74, 1.09)	1.07 (0.88, 1.30)
Patients with ≥1 observed pregnancy in the cohort (n=381)		
Unexposed	1.0 (ref)	1.0 (ref)
Pregnancy	1.54 (1.22, 1.90)	1.85 (1.43, 2.35)
Postpartum	0.99 (0.79, 1.23)	1.21 (0.96, 1.53)

[A]flare defined as change in ≥4 from SELENA SLEDAI score at previous visit
[B]Counting process Cox proportional hazards model assumes the order of the events of flares did not need to be taken into consideration
[C]Stratified Cox model is a conditional model that does not assume independence of multiple events of flares and allows different baseline hazards based on the number of previous flares a patient experienced
CI: confidence interval; HR: hazard ratio; SLE: systemic lupus erythematosus; SLEDAI: SLE Disease Activity Index

REFERENCES

1. Danchenko N, Satia JA, Anthony MS. Epidemiology of systemic lupus erythematosus: a comparison of worldwide disease burden. Lupus 2006;15(5):308-18.

2. Lim SS, Bayakly AR, Helmick CG, Gordon C, Easley KA, Drenkard C. The Incidence and Prevalence of Systemic Lupus Erythematosus, 2002–2004: The Georgia Lupus Registry. Arthritis Rheumatol 2014;66(2):357-68.

3. Somers EC, Marder W, Cagnoli P, et al. Population-Based Incidence and Prevalence of Systemic Lupus Erythematosus: The Michigan Lupus Epidemiology and Surveillance Program. Arthritis Rheumatol 2014;66(2):369-78.

4. Ruiz-Irastorza G, Khamashta MA. Lupus and pregnancy: integrating clues from the bench and bedside. Eur J Clin Invest 2011;41(6):672-8.

5. Andrade RM, McGwin G, Jr., Alarcon GS, et al. Predictors of post-partum damage accrual in systemic lupus erythematosus: data from LUMINA, a multiethnic US cohort (XXXVIII). Rheumatology 2006;45(11):1380-4.

6. Clark CA, Spitzer KA, Nadler JN, Laskin CA. Preterm deliveries in women with systemic lupus erythematosus. J Rheumatol 2003;30(10):2127-32.

7. Clowse ME, Magder LS, Witter F, Petri M. The impact of increased lupus activity on obstetric outcomes. Arthritis Rheum 2005;52(2):514-21.

8. IOM (Institute of Medicine) and NRC (National Research Council). 2009. Weight Gain During Pregnancy: Reexamining the Guidelines. Washington, DC: The National Academies Press.

9. Beyerlein A, Lack N, von Kries R. Within-population average ranges compared with Institute of Medicine recommendations for gestational weight gain. Obstet Gynecol 2010;116(5):1111-8.

10. Savitz DA, Stein CR, Siega-Riz AM, Herring AH. Gestational weight gain and birth outcome in relation to prepregnancy body mass index and ethnicity. Ann Epidemiol 2011;21(2):78-85.

11. Simas TAM, Liao X, Garrison A, Sullivan GMT, Howard AE, Hardy JR. Impact of updated Institute of Medicine Guidelines on prepregnancy body mass index categorization, gestational weight gain recommendations, and needed counseling. J Womens Health 2011;20(6):837-44.

12. Tan EM, Cohen AS, Fries JF, et al. The 1982 revised criteria for the classification of systemic lupus erythematosus. Arthritis Rheum 1982;25(11):1271-7.

13. Hochberg MC. Updating the American college of rheumatology revised criteria for the classification of systemic lupus erythematosus. Arthritis Rheum 1997;40(9):1725.

14. Fernández M, Alarcón GS, Rosa JC-a, et al. A multiethnic, multicenter cohort of patients with systemic lupus erythematosus (SLE) as a model for the study of ethnic disparities in SLE. Arthritis Care Res 2007;57(4):576-84.

15. Somers EC, Thomas SL, Smeeth L, et al. Incidence of systemic lupus erythematosus in the United Kingdom, 1990-1999. Arthritis Rheumatol 2007;57(4):612-8.

16. Chakravarty EF, Bush TM, Manzi S, Clarke AE, Ward MM. Prevalence of adult systemic lupus erythematosus in California and Pennsylvania in 2000: estimates obtained using hospitalization data. Arthritis Rheum 2007;56(6):2092-4.

17. Uribe AG, Alarcón GS. Ethnic disparities in patients with systemic lupus erythematosus. Curr Rheumatol Rep 2003;5(5):364-9.

18. Gladman DD, Urowitz MB, Rahman P, Ibañez D, Tam LS. Accrual of organ damage over time in patients with systemic lupus erythematosus. J Rheumatol 2003;30(9):1955-9.

19. Alarcón GS, Roseman JM, McGwin G, Jr, et al. Systemic lupus erythematosus in three ethnic groups. XX. Damage as a predictor of further damage. Rheumatology 2004;43(2):202-5.

20. Stoll T, Sutcliffe N, Mach J, Klaghofer R, Isenberg DA. Analysis of the relationship between disease activity and damage in patients with systemic lupus erythematosus--a 5-yr prospective study. Rheumatology 2004;43(8):1039-44.

21. Urowitz MB, Gladman D, Ibañez D, et al. Accumulation of coronary artery disease risk factors over three years: data from an international inception cohort. Arthritis Care Res 2008;59(2):176-80.

22. Sutcliffe N, Clarke AE, Gordon C, Farewell V, Isenberg DA. The association of socio-economic status, race, psychosocial factors and outcome in patients with systemic lupus erythematosus. Rheumatology 1999;38(11):1130-7.

23. Bertoli AM, Vila LM, Apte M, et al. Systemic lupus erythematosus in a multiethnic US Cohort LUMINA XLVIII: factors predictive of pulmonary damage. Lupus 2007;16(6):410-7.

24. Bertoli AM, Vilá LM, Reveille JD, Alarcón GS, LUMINA Study Group. Systemic lupus erythaematosus in a multiethnic US cohort (LUMINA) LIII: disease expression and outcome in acute onset lupus. Ann Rheum Dis 2008;67(4):500-4.

25. Chaiamnuay S, Bertoli AM, Roseman JM, et al. African-American and Hispanic ethnicities, renal involvement and obesity predispose to hypertension in systemic lupus erythematosus: results from LUMINA, a multiethnic cohort (LUMINAXLV). Ann Rheum Dis 2007;66(5):618-22.

26. Boers A, Li Q, Wong M, Miller M, Littlejohn G. Differences in SLE disease activity between patients of Caucasian and South-East Asian/Chinese background in an Australian hospital. APLAR Journal of Rheumatology 2006;9(1):43-8.

27. Rhew EY, Manzi SM, Dyer AR, et al. Differences in subclinical cardiovascular disease between African American and Caucasian women with systemic lupus erythematosus. Transl Res 2009;153(2):51-9.

28. Johnson SR, Urowitz MB, Ibañez D, Gladman DD. Ethnic variation in disease patterns and health outcomes in systemic lupus erythematosus. J Rheumatol 2006;33(10):1990-5.

29. Stoll T, Sutcliffe N, Klaghofer R, Isenberg DA. Do present damage and health perception in patients with systemic lupus erythematosus predict extent of future damage?: a prospective study. Ann Rheum Dis 2000;59(10):832-5.

30. Yee CS, Hussein H, Skan J, Bowman S, Situnayake D, Gordon C. Association of damage with autoantibody profile, age, race, sex and disease duration in systemic lupus erythematosus. Rheumatology 2003;42(2):276-9.

31. Peschken CA, Katz SJ, Silverman E, et al. The 1000 Canadian Faces of Lupus: Determinants of Disease Outcome in a Large Multiethnic Cohort. J Rheumatol 2009:-.

32. Ghaussy NO, Sibbitt W, Bankhurst AD, Qualls CR. The effect of race on disease activity in systemic lupus erythematosus. J Rheumatol 2004;31(5):915-9.

33. Johnson AE, Gordon C, Palmer RG, Bacon PA. The prevalence and incidence of systemic lupus erythematosus in Birmingham, England. Relationship to ethnicity and country of birth. Arthritis Rheum 1995;38(4):551-8.

34. Peschken CA, Esdaile JM. Systemic lupus erythematosus in North American Indians: a population based study. J Rheumatol 2000;27(8):1884-91.

35. Lau CS, Yin G, Mok MY. Ethnic and geographical differences in systemic lupus erythematosus: an overview. Lupus 2006;15(11):715-9.

36. Karpouzas GA, Kitridou RC. The mother in systemic lupus erythematosus. In: Wallace DJ, Hahn BH, eds. Dubois' Lupus Erythematosus. Philadelphia, PA: Lippincott Williams & Wilkins, 2007:992-1038.

37. Lateef A, Petri M. Managing lupus patients during pregnancy. Best Pract Res Clin Rheumatol 2013;27(3):435-47.

38. Østensen M, Khamashta M, Lockshin M, et al. Anti-inflammatory and immunosuppressive drugs and reproduction. Arthritis Res Ther 2006;8(3):209.

39. Clowse MEB, Magder L, Witter F, Petri M. Hydroxychloroquine in lupus pregnancy. Arthritis Rheum 2006;54(11):3640-7.

40. Bermas BL, Hill JA. Effects of immunosuppressive drugs during pregnancy. Arthritis Rheum 1995;38(12):1722-32.

41. Cowchock FS, Reece EA, Balaban D, Branch DW, Plouffe L. Repeated fetal losses associated with antiphospholipid antibodies: a collaborative randomized trial comparing prednisone with low-dose heparin treatment. Am J Obstet Gynecol 1992;166(5):1318-23.

42. Silver RK, MacGregor SN, Sholl JS, Hobart JM, Neerhof MG, Ragin A. Comparative trial of prednisone plus aspirin versus aspirin alone in the treatment of anticardiolipin antibody-positive obstetric patients. Am J Obstet Gynecol 1993;169(6):1411-7.

43. Laskin CA, Bombardier C, Hannah ME, et al. Prednisone and aspirin in women with autoantibodies and unexplained recurrent fetal loss. NEJM 1997;337(3):148-54.

44. Clark CA, Spitzer KA, Laskin CA. Decrease in pregnancy loss rates in patients with systemic lupus erythematosus over a 40-year period. J Rheumatol 2005;32(9):1709-12.

45. Coletta J, Simpson LL. Maternal medical disease and stillbirth. Clin Obstet Gynecol 2010;53(3):607-16

46. CDC. Fetal Deaths. 2012. (http://www.cdc.gov/nchs/fetal_death.htm). (Accessed 2014).

47. Wilcox AJ. Fertility and Pregnancy: An Epidemiologic Perspective. New York: Oxford University Press; 2010.

48. Ambrósio P, Lermann R, Cordeiro A, Borges A, Nogueira I, Serrano F. Lupus and Pregnancy—15 Years of Experience in a Tertiary Center. Clin Rev Allergy Immunol 2010;38(2):77-81.

49. Brucato A, Doria A, Frassi M, et al. Pregnancy outcome in 100 women with autoimmune diseases and anti-Ro/SSA antibodies: a prospective controlled study. Lupus 2002;11(11):716-21.

50. Carvalheiras G, Vita P, Marta S, et al. Pregnancy and systemic lupus erythematosus: review of clinical features and outcome of 51 pregnancies at a single institution. Clin Rev Allergy Immunol 2010;38(2):302-6.

51. Cavallasca JA, Laborde HA, Ruda-Vega H, Nasswetter GG. Maternal and fetal outcomes of 72 pregnancies in Argentine patients with systemic lupus erythematosus (SLE). Clin Rheumatol 2008;27(1):41-6.

52. Chakravarty EF, Colón I, Langen ES, et al. Factors that predict prematurity and preeclampsia in pregnancies that are complicated by systemic lupus erythematosus. Am J Obstet Gynecol 2005;192(6):1897-904.

53. Cortés-Hernández J, Ordi-Ros J, Paredes F, Casellas M, Castillo F, Vilardell-Tarres M. Clinical predictors of fetal and maternal outcome in systemic lupus erythematosus: a prospective study of 103 pregnancies. Rheumatology 2002;41(6):643-50.

54. Georgiou PE, Politi EN, Katsimbri P, Sakka V, Drosos AA. Outcome of lupus pregnancy: a controlled study. Rheumatology 2000;39(9):1014-9.

55. Andrade R, Sanchez ML, Alarcón GS, et al. Adverse pregnancy outcomes in women with systemic lupus erythematosus from a multiethnic US cohort: LUMINA (LVI). Clin Exp Rheumatol 2008;26(2):268-74.

56. Clowse ME, Magder LS, Witter F, Petri M. Early risk factors for pregnancy loss in lupus. Obstet Gynecol 2006;107(2 Part 1):293-9.

57. Gladman DD, Tandon A, Ibañez D, Urowitz MB. The effect of lupus nephritis on pregnancy outcome and fetal and maternal complications. J Rheumatol 2010;37(4):754-8.

58. Ventura SJ, Curtin SC, Abma JC, Henshaw SK. Estimated pregnancy rates and rates of pregnancy outcomes for the United States, 1990–2008. National Vital Statistics Reports 2012;60(7).

59. Julkunen H, Jouhikainen T, Kaaja R, et al. Fetal outcome in lupus pregnancy: a retrospective case-control study of 242 pregnancies in 112 patients. Lupus 1993;2(2):125-31.

60. Blencowe H, Cousens S, Oestergaard MZ, et al. National, regional, and worldwide estimates of preterm birth rates in the year 2010 with time trends since 1990 for selected countries: a systematic analysis and implications. Lancet 2012;379:2162-72.

61. Martin J, Hamilton B, Sutton P, et al. Births: Final data for 2006. National Vital Statistics Reports 2009;57(7).

62. Goldenberg RL, McClure EM. The epidemiology of preterm birth. In: Berghella V, ed. Preterm Birth: Prevention and Management. West Sussex, UK: John Wiley & Sons Ltd, 2010:22-39.

63. Petrou S, Mehta Z, Hockley C, Cook-Mozaffari P, Henderson J, Goldacre M. The impact of preterm birth on hospital inpatient admissions and costs during the first 5 years of life. Pediatrics 2003;112(6):1290-7.

64. Mecacci F, Bianchi B, Pieralli A, et al. Pregnancy outcome in systemic lupus erythematosus complicated by anti-phospholipid antibodies. Rheumatology 2009;48(3):246-9.

65. Barnabe C, Faris P, Hude Q. Canadian pregnancy outcomes in rheumatoid arthritis and systemic lupus. Int J Rheumatol 2011.

66. Martin JA, Hamilton BE, Osterman MJ, Curtin SC. Births: Final Data for 2012. National Vital Statistics Reports 2013;62(9).

67. Mathews T, MacDorman M. Infant mortality statistics from the 2009 period linked birth/infant death data set. National Vital Statistics Reports 2013;61(8).

68. Hediger ML, Joseph KS. Fetal growth: measurement and evaluation. In: Buck Louis GM, Platt RW, eds. Reproductive and Perinatal Epidemiology. New York, NY: Oxford University Press, 2011:168-85.

69. Pipkin F. Physiological changes in pregnancy. In: Symonds I, Arulkumaran S, eds. Essential Obstetrics and Gynaecology, Fifth Edition: Churchill Livingstone, 2013:23-40.

70. Lederman SA, Paxton A, Heymsfield SB, Wang J, Thornton J, Pierson RN. Maternal body fat and water during pregnancy: do they raise infant birth weight? Am J Obstet Gynecol 1999;180(1):235-40.

71. Lederman SA, Paxton A, Heymsfield SB, Wang J, Pierson RN. Body fat and water changes during pregnancy in women with different body weight and weight gain. Obstet Gynecol 1997;90(4, Part 1):483-8.

72. Carmichael S, Abrams B, Selvin S. The pattern of maternal weight gain in women with good pregnancy outcomes. Am J Public Health 1997;87(12):1984-8.

73. Crane JM, White J, Murphy P, Burrage L, Hutchens D. The effect of gestational weight gain by body mass index on maternal and neonatal outcomes. J Obstet Gynaecol Can 2009;31(1):28-35.

74. Frederick IO, Williams MA, Sales AE, Martin DP, Killien M. Pre-pregnancy body mass index, gestational weight gain, and other maternal characteristics in relation to infant birth weight. Matern Child Health J 2008;12(5):557-67.

75. Nohr EA, Vaeth M, Baker JL, Sørensen TI, Olsen J, Rasmussen KM. Combined associations of prepregnancy body mass index and gestational weight gain with the outcome of pregnancy. Am J Clin Nutr 2008;87(6):1750-9.

76. Hillier TA, Pedula KL, Vesco KK, et al. Excess gestational weight gain: modifying fetal macrosomia risk associated with maternal glucose. Obstet Gynecol 2008;112(5):1007-14.

77. Ludwig DS, Currie J. The association between pregnancy weight gain and birthweight: a within-family comparison. Lancet 2010;376(9745):984-90.

78. Kiel DW, Dodson EA, Artal R, Boehmer TK, Leet TL. Gestational weight gain and pregnancy outcomes in obese women: how much is enough? Obstet Gynecol 2007;110(4):752-8.

79. Hellerstedt WL, Himes JH, Story M, Alton IR, Edwards LE. The effects of cigarette smoking and gestational weight change on birth outcomes in obese and normal-weight women. Am J Public Health 1997;87(4):591-6.

80. Edwards LE, Hellerstedt WL, Alton IR, Story M, Himes JH. Pregnancy complications and birth outcomes in obese and normal-weight women: effects of gestational weight change. Obstet Gynecol 1996;87(3):389-94.

81. Caulfield LE, Stoltzfus RJ, Witter FR. Implications of the Institute of Medicine weight gain recommendations for preventing adverse pregnancy outcomes in black and white women. Am J Public Health 1998;88(8):1168-74.

82. Stotland NE, Cheng YW, Hopkins LM, Caughey AB. Gestational weight gain and adverse neonatal outcome among term infants. Obstet Gynecol 2006;108(3, Part 1):635-43.

83. Parker JD, Abrams B. Prenatal weight gain advice: an examination of the recent prenatal weight gain recommendations of the Institute of Medicine. Obstet Gynecol 1992;79(5 (Pt 1)):664-9.

84. DeVader SR, Neeley HL, Myles TD, Leet TL. Evaluation of gestational weight gain guidelines for women with normal prepregnancy body mass index. Obstet Gynecol 2007;110(4):745-51.

85. Cogswell ME, Serdula MK, Hungerford DW, Yip R. Gestational weight gain among average-weight and overweight women—what is excessive? Am J Obstet Gynecol 1995;172(2):705-12.

86. Bianco AT, Smilen SW, Davis Y, Lopez S, Lapinski R, Lockwood CJ. Pregnancy outcome and weight gain recommendations for the morbidly obese woman. Obstet Gynecol 1998;91(1):97-102.

87. Schieve LA, Cogswell ME, Scanlon KS. An empiric evaluation of the Institute of Medicine's pregnancy weight gain guidelines by race. Obstet Gynecol 1998;91(6):878-84.

88. Thorsdottir I, Torfadottir JE, Birgisdottir BE, Geirsson RT. Weight gain in women of normal weight before pregnancy: complications in pregnancy or delivery and birth outcome. Obstet Gynecol 2002;99(5, Part 1):799-806.

89. Hedderson MM, Weiss NS, Sacks DA, et al. Pregnancy weight gain and risk of neonatal complications: macrosomia, hypoglycemia, and hyperbilirubinemia. Obstet Gynecol 2006;108(5):1153-61.

90. Nielsen JN, O'Brien KO, Witter FR, et al. High gestational weight gain does not improve birth weight in a cohort of African American adolescents. Am J Clin Nutr 2006;84(1):183-9.

91. Siega-Riz AM, Adair LS, Hobel CJ. Maternal underweight status and inadequate rate of weight gain during the third trimester of pregnancy increases the risk of preterm delivery. J Nutr 1996;126(1):146-53.

92. Drehmer M, Duncan BB, Kac G, Schmidt MI. Association of second and third trimester weight gain in pregnancy with maternal and fetal outcomes. PLoS ONE 2013;8(1):e54704.

93. Wise LA, Palmer JR, Heffner LJ, Rosenberg L. Prepregnancy body size, gestational weight gain, and risk of preterm birth in African-American women. Epidemiology 2010;21(2):243-52.

94. Oken E, Kleinman KP, Belfort MB, Hammitt JK, Gillman MW. Associations of gestational weight gain with short- and longer-term maternal and child health outcomes. Am J Epidemiol 2009;170(2):173-80.

95. Lloyd-Jones DM, Hong Y, Labarthe D, et al. Defining and setting national goals for cardiovascular health promotion and disease reduction the American Heart Association’s Strategic Impact Goal through 2020 and beyond. Circulation 2010;121(4):586-613.

96. Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. Executive summary of the third report of the National Cholesterol Education Program (NCEP) expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (Adult Treatment Panel III). JAMA 2001;285(19):2486-97.

97. Chobanian AV, Bakris GL, Black HR, et al. The seventh report of the joint national committee on prevention, detection, evaluation, and treatment of high blood pressure: the JNC 7 report. JAMA 2003;289(19):2560-71.

98. American Diabetes Association. Diagnosis and classification of diabetes mellitus. Diabetes Care 2008;31(Supplement 1):S55-S60.

99. Bertoli AM, Alarcón GS, Calvo-Alén J, Fernández M, Vilá LM, Reveille JD. Systemic lupus erythematosus in a multiethnic US cohort: Clinical features, course, and outcome in patients with late-onset disease. Arthritis Rheum 2006;54(5):1580-7.

100. Urowitz MB, Gladman DD. Atherosclerosis and Lupus -- The SLICC study. Lupus 2007;16(12):925-8.

101. Urowitz MB, Gladman D, Ibañez D, et al. Clinical manifestations and coronary artery disease risk factors at diagnosis of systemic lupus erythematosus: data from an international inception cohort. Lupus 2007;16(9):731-5.

102. Greenberg AS, Obin MS. Obesity and the role of adipose tissue in inflammation and metabolism. Am J Clin Nutr 2006;83(2):461S-5S.

103. King JC. Maternal obesity, metabolism, and pregnancy outcomes. Annu Rev Nutr 2006;26:271-91.

104. Godfrey KM, Barker DJ. Fetal programming and adult health. Public Health Nutr 2001;4(2b):611-24.

105. Bhattacharya S, Campbell DM, Liston WA, Bhattacharya S. Effect of body mass index on pregnancy outcomes in nulliparous women delivering singleton babies. BMC Public Health 2007;7(1):168.

106. Ehrenberg HM, Mercer BM, Catalano PM. The influence of obesity and diabetes on the prevalence of macrosomia. Am J Obstet Gynecol 2004;191(3):964-8.

107. Lu GC, Rouse DJ, DuBard M, Cliver S, Kimberlin D, Hauth JC. The effect of the increasing prevalence of maternal obesity on perinatal morbidity. Am J Obstet Gynecol 2001;185(4):845-9.

108. Gilbert WM, Young AL, Danielsen B. Pregnancy outcomes in women with chronic hypertension: a population-based study. J Reprod Med 2007;52(11):1046-51.

109. Catov JM, Nohr EA, Olsen J, Ness RB. Chronic hypertension related to risk for preterm and term small-for-gestational-age births. Obstet Gynecol. 2008;112(2 Pt 1):290-6.

110. Chatzi L, Plana E, Daraki V, et al. Metabolic syndrome in early pregnancy and risk of preterm birth. Am J Epidemiol 2009;170(7):829-36.

111. Haelterman E, Bréart G, Paris-Liado J, Dramaix M, Tchobroutsky C. Effect of uncomplicated chronic hypertension on the risk of small-for-gestational age birth. Am J Epidemiol 1997;145(8):689-95.

112. Catov JM, Bodnar LM, Kip KE, et al. Early pregnancy lipid concentrations and spontaneous preterm birth. Am J Obstet Gynecol 2007;197(6):610.e1-.e7.

113. Catov JM, Bodnar LM, Ness RB, Barron SJ, Roberts JM. Inflammation and dyslipidemia related to risk of spontaneous preterm birth. Am J Epidemiol 2007;166(11):1312-9.

114. Sattar N, Greer IA. Pregnancy complications and maternal cardiovascular risk: opportunities for intervention and screening? BMJ 2002;325:157-60.

115. Petri M, Buyon J, Kim M. Classification and definition of major flares in SLE clinical trials. Lupus 1999;8(8):685-91.

116. Buyon JP, Petri MA, Kim MY, et al. The effect of combined estrogen and progesterone hormone replacement therapy on disease activity in systemic lupus erythematosus: a randomized trial. Ann Inter Med 2005;142(12 Part 1):953-62.

117. Petri M, Kim MY, Kalunian KC, et al. Combined oral contraceptives in women with systemic lupus erythematosus. NEJM 2005;353(24):2550-8.

118. Bombardier C, Gladman DD, Urowitz MB, et al. Derivation of the SLEDAI. A disease activity index for lupus patients. Arthritis Rheum 1992;35(6):630-40.

119. Symmons DPM, Coppock JS, Bacon PA, et al. Development and assessment of a computerized index of clinical disease activity in systemic lupus erythematosus. QJM 1988;69(2):927-37.

120. Isenberg DA, Rahman A, Allen E, et al. BILAG 2004. Development and initial validation of an updated version of the British Isles Lupus Assessment Group's disease activity index for patients with systemic lupus erythematosus. Rheumatology 2005;44(7):902-6.

121. Fellows of Harvard College. SLE Activity Measure-Revised (SLAM- R). 1988. Revised July 1991

122. Bae SC, Koh HK, Chang DK, Kim MH, Park JK, Kim SY. Reliability and validity of systemic lupus activity measure-revised (SLAM-R) for measuring clinical disease activity in systemic lupus erythematosus. Lupus 2001;10(6):405-9.

123. Vitali C, Bencivelli W, Isenberg DA, et al. Disease activity in systemic lupus erythematosus: report of the Consensus Study Group of the European Workshop for Rheumatology Research. I. A descriptive analysis of 704 European lupus patients. European Consensus Study Group for Disease Activity in SLE. Clin Exp Rheumatol 1991;10(5):527-39.

124. Bencivelli W, Vitali C, Isenberg DA, et al. Disease activity in systemic lupus erythematosus: report of the Consensus Study Group of the European Workshop for Rheumatology Research. III. Development of a computerised clinical chart and its application to the comparison of different indices of disease activity. The European Consensus Study Group for Disease Activity in SLE. Clin Exp Rheumatol 1992;10(5):549-54.

125. Vitali C, Bencivelli W, Isenberg DA, et al. Disease activity in systemic lupus erythematosus: report of the Consensus Study Group of the European Workshop for Rheumatology Research. II. Identification of the variables indicative of disease activity and their use in the development of an activity score. The European Consensus Study Group for Disease Activity in SLE. Clin Exp Rheumatol 1991;10(5):541-7.

126. Petri M, Howard D, Repke J. Frequency of lupus flare in pregnancy: the Hopkins Lupus Pregnancy Center experience. Arthritis Rheum 1991;34(12):1538-45.

127. Ruiz-Irastorza G, Lima F, Alves J, et al. Increased rate of lupus flare during pregnancy and the puerperium: a prospective study of 78 pregnancies. Rheumatology 1996;35(2):133-8.

128. Urowitz MB, Gladman DD, Farewell VT, Stewart J, McDonald J.. Lupus and pregnancy studies. Arthritis Rheum 1993;36(10):1392-7.

129. Zulman JI, Talal N, Hoffman GS, Epstein WV. Problems associated with the management of pregnancies in patients with systemic lupus erythematosus. J Rheumatol 1980;7(1):37.

130. Garsenstein M, Pollak VE, Kark RM. Systemic lupus erythematosus and pregnancy. NEJM 1962;267(4):165-9.

131. Wong KL, Chan FY, Lee CP. Outcome of pregnancy in patients with systemic lupus erythematosus: a prospective study. Arc Intern Med 1991;151(2):269-73.

132. Lockshin MD, Reinitz E, Druzin ML, Murrman M, Estes D. Lupus pregnancy: case-control prospective study demonstrating absence of lupus exacerbation during or after pregnancy. Am J Med 1984;77(5):893-8.

133. Petri M, Orbai AM, Alarcón GS, et al. Derivation and validation of the Systemic Lupus International Collaborating Clinics classification criteria for systemic lupus erythematosus. Arthritis Rheum 2012;64(8):2677-86.

134. Oken E, Kleinman KP, Rich-Edwards J, Gillman MW. A nearly continuous measure of birth weight for gestational age using a United States national reference. BMC Pediatrics 2003;3(1):6.

135. Petri M, Hellmann D, Hochberg M. Validity and reliability of lupus activity measures in the routine clinic setting. J Rheumatol 1992;19(1):53-9.

136. Liang KY, Zeger SL. Longitudinal data analysis using generalized linear models. Biometrika 1986;73(1):13-22.

137. Fitzmaurice GM, Laird NM, Ware JH. Applied Longitudinal Analysis. John Wiley & Sons, Inc., 2004:326-8.

138. Efron B, Tibshirani RJ. An Introduction to the Bootstrap. CRC press; 1994.

139. Margerison Zilko CE, Rehkopf D, Abrams B. Association of maternal gestational weight gain with short- and long-term maternal and child health outcomes. Am J Obstet Gynecol 2010;202(6):574.e1-.e8.

140. Oken E, Taveras EM, Kleinman KP, Rich-Edwards JW, Gillman MW. Gestational weight gain and child adiposity at age 3 years. Am J Obstet Gynecol 2007;196(4):322.e1-.e8.

141. Deputy NP, Sharma AJ, Kim SY, Hinkle SN. Prevalence and characteristics associated with gestational weight gain adequacy. Obstet Gynecol 2015;125(4):773-81.

142. Johnson JL, Farr SL, Dietz PM, Sharma AJ, Barfield WD, Robbins CL. Trends in gestational weight gain: the Pregnancy Risk Assessment Monitoring System, 2000–2009. Am J Obstet Gynecol 2015;212(6):806.e1-.e8.

143. Podymow T, August P, Akbari A. Management of renal disease in pregnancy. Obstet Gynecol Clin North Am 2010;37(2):195-210.

144. Baxter JD, Forsham PH. Tissue effects of glucocorticoids. Am J Med 1972;53(5):573-89.

145. Russell A, Gillespie S, Satya S, Gaudet LM. Assessing the accuracy of pregnant women in recalling pre-pregnancy weight and gestational weight gain. JOGC 2013;35(9):802-9.

146. Petri M, Daly R, Pushparajah D. Healthcare costs of pregnancy in systemic lupus erythematosus: retrospective observational analysis from a US health claims database. J Med Econ 2015 2;18(11):967-73.

147. Clowse MEB, Jamison M, Myers E, James AH. A national study of the complications of lupus in pregnancy. AJOG 2008;199(2):127.e1-.e6.

148. Cedergren MI. Maternal morbid obesity and the risk of adverse pregnancy outcome. Obstet Gynecol 2004;103(2):219-24.

149. Wolf M, Kettyle E, Sandler L, Ecker JL, Roberts J, Thadhani R. Obesity and preeclampsia: the potential role of inflammation. Obstet Gynecol 2001;98(5, Part 1):757-62.

150. Rosenberg TJ, Garbers S, Chavkin W, Chiasson MA. Prepregnancy weight and adverse perinatal outcomes in an ethnically diverse population. Obstet Gynecol 2003;102(5, Part 1):1022-7.

151. Solomon CG, Willett WC, Carey VJ, et al. A prospective study of pregravid determinants of gestational diabetes mellitus. JAMA 1997;278(13):1078-83.

152. Potter JM, Nestel PJ. The hyperlipidemia of pregnancy in normal and complicated pregnancies. Am J Obstet Gynecol 1979;133(2):165-70.

153. Fattah C, Farah N, Barry SC, O'Connor N, Stuart B, Turner MJ. Maternal weight and body composition in the first trimester of pregnancy. Acta Obstet Gynecol Scand 2010;89(7):952-5.

154. Stuebe AM, Landon MB, Lai Y, et al. Maternal BMI, glucose tolerance, and adverse pregnancy outcomes. Am J Obstet Gynecol 2012;207(1):62.e1-.e7.

155. Khashan AS, Kenny LC. The effects of maternal body mass index on pregnancy outcome. Eur J Epidemiol 2009;24(11):697-705.

156. Tinker SC, Hamner HC, Berry RJ, Bailey LB, Pfeiffer CM. Does obesity modify the association of supplemental folic acid with folate status among nonpregnant women of childbearing age in the United States? Birth Defects Res A Clin Mol Teratol 2012;94(10):749-55.

157. Chakravarty EF, Nelson L, Krishnan E. Obstetric hospitalizations in the United States for women with systemic lupus erythematosus and rheumatoid arthritis. Arthritis Rheum 2006;54(3):899-907.

158. Haas JS, Fuentes-Afflick E, Stewart AL, et al. Prepregnancy health status and the risk of preterm delivery. Arch Pediatr Adolesc Med 2005;159(1):58-63.

159. Nohr EA, Bech BH, Vaeth M, Rasmussen KM, Henriksen TB, Olsen J. Obesity, gestational weight gain and preterm birth: a study within the Danish National Birth Cohort. Paediatr Perinat Epidemiol 2007;21(1):5-14.

160. Smith GC, Shah I, Pell JP, Crossley JA, Dobbie R. Maternal obesity in early pregnancy and risk of spontaneous and elective preterm deliveries: a retrospective cohort study. Am J Public Health. 2007;97(1):157-62.

161. Hendler I, Goldenberg RL, Mercer BM, et al. The Preterm Prediction study: association between maternal body mass index and spontaneous and indicated preterm birth. Am J Obstet Gynecol 2005;192(3):882-6.

162. Catov JM, Ness RB, Wellons MF, Jacobs DR, Roberts JM, Gunderson EP. Prepregnancy lipids related to preterm birth risk: the coronary artery risk development in young adults study. J Clin Endocrinol Metab 2010;95(8):3711-8.

163. Petri M, Howard D, Repke J, Goldman DW. The Hopkins Lupus Pregnancy Center: 1987–1991 update. Am J Reprod Immunol 1992;28(3-4):188-91.

164. Soh MC, Nelson-Piercy C, Dib F, Westgren M, McCowan L, Pasupathy D. Association between pregnancy outcomes and cardiovascular deaths in women with systemic lupus erythematosus utilising Swedish population registries. Arthritis Rheumatol. 2015;67(9):2376-82

165. Therneau TM, Grambsch PM. Modeling survival data: extending the Cox model. Springer Science & Business Media; 2000.

166. Mintz G, Niz J, Gutierrez G, Garcia-Alonso A, Karchmer S. Prospective study of pregnancy in systemic lupus erythematosus. Results of a multidisciplinary approach. J Rheumatol 1986;13(4):732-9.